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Endocrine Studies on Human Hermaphrodites and Their Bearing on the Interpretation of Homosexuality[1]

[Hermaphroditism]

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HUMAN HERMAPHRODITES fall into a number of discrete classes according to morphological appearance and probable causation (1). The origin of three is related to neoplastic growth of endocrine tissues, such as adrenal cortex (adrenogenital syndrome), ovarian medulla (arrhenoblastoma) and testicular blastema (chorioepithelioma of the testis). Their pathological nature, as well as the immediate causative factors, are easily recognizable. The afflicted individuals are distinctly *sick patients*, and operative removal of the tumors, if performed at the proper time, may restore normalcy, even with full reproductive capacity.

More enigmatical is the nature of sex intergrades of healthy appearance and without endocrine disturbances that might point directly toward the cause of their condition. However, it is fairly certain that many, possibly the large majority, of the cases have some hereditary background and that, with respect to the sex which suffers transformation, this hereditary group is divided in two classes. In the first one, the daughters are normal while *the sons are hermaphrodites*. Transmission of the character is therefore possible only in the female line. The available records of affected families indicate that a dominant gene causes heterozygous mothers to produce hormones or hormone-like substances which, in early pregnancy, effect a feminization of male fetuses. In accordance with expectations, half of the daughters prove to be carriers of this modifying gene. In typical cases, undescended testicles are present, together with ovarian tubes, uterus and vagina. At the time of puberty, male secondary sex characters begin to appear, with partial change of voice, male type of hair growth and enlargement of the clitoris. The complete range of variability of morphological features is not yet known (for complete discussion and references see reference 1).

It appears now that there exists a second class of hereditary hermaphrodism in which the female sex becomes afflicted. Within the last 4 years, two individuals clearly of this type presented themselves at the University Hospitals for remedial surgery. They had been reared as sisters. There are altogether

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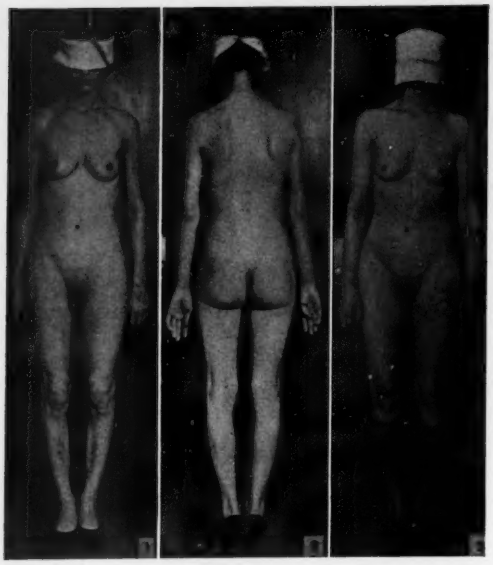

Fig. 1, 2. PATIENT 1. In preparation of the first operation, the pubic hair had been removed; the feminine straight top of the escutcheon is faintly visible. Fig. 3. PATIENT 1, 17 months after the second operation.

four siblings in this family: two normal boys and the two hermaphrodites. One boy is married and is the father of a son. In public appearance, both hermaphrodites give the impression of normal girls. Their parents also considered them to be predominantly feminine, and reared them as girls. They had, when seen at the ages of 26 and 24, respectively, distinctly feminine voices. The skin was smooth, no beard was growing, and the breasts were well developed. Their interests also were of feminine orientation. Both were married, apparently without having a clear idea that their abnormality would interfere with marital life. The first patient came directly under our observation, the second only after having received treatment in another hospital. This report is therefore mainly based on the first patient, though it has been ascertained that the second is of nearly identical type.

Description of Patient 1

The older 'sister,' *patient 1*, came to the University Hospitals for the expressed purpose of the removal of two lumps which "got in her way when she danced with a man." 'She' assured the doctors that no other member of the family was similarly afflicted. Clinical examination revealed (fig. 1–3), in addition to the above data, dome-shaped breasts with well-developed nipples. The pubic hair presented a typical straight-topped feminine escutcheon. The chest was relatively small, and the hips wide, but not quite as broad as the shoulders. The legs and arms were relatively long and less feminine than the rest of the body. The patient had been engaged for some time in strenuous physical work and part of the muscular development may be attributed to exercise. Roentgenograms, made after the initial admission, revealed a bony pelvis of intermediate sexual type (fig. 4).

Curiously enough, this partly eunuchoid, partly feminine body was found associated with sex organs of predominantly male character (fig. 5). A bifid scrotum contained two well-descended testes (proved by bilateral biopsy), the right one larger than average size. The penis was small, about 5.5 cm. long, including the glans which measured 1.5 cm. It was completely formed except for the absence of the urethra, the meatus of which opened in a depression about two cm. below the base of the penis. Bilateral to this ori-

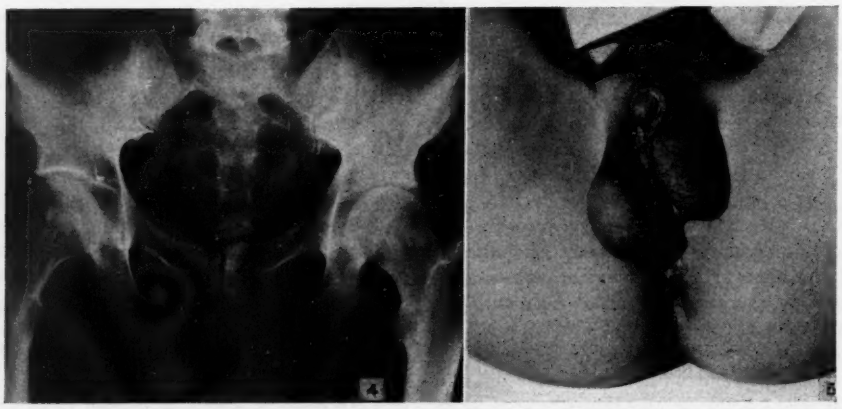

Fig. 4. PELVIS of *patient 1*. Fig. 5. EXTERNAL GENITAL ORGANS OF *patient 1*.

fice, there were small folds of tissue which continued anteriorly to form a frenulum for the penis. No vagina was evident and no prostate gland could be palpated on rectal examination.

Exploratory laparotomy proved the complete absence of female internal organs (uterus, tubes and ovaries). The cul-de-sac was entirely of male type, and structures closely resembling vasa deferentia were seen along each pelvic wall in a position normal for them. Biopsy specimens of the sex glands contained a few abnormal spermatozoa. The majority of seminal tubules were sterile.

Very interesting was the psychological attitude of this patient. 'She' had never been attracted by girls and, in spite of the failure of the first marriage, was in love with a man again. The medical adviser's proposal to make a surgical correction of hypospadias and to change the legal sex was very decidedly rejected. To the contrary, the patient insisted on having the external male organs removed and an artificial vagina made. She hoped that operation would bring about a change to enable her definitely to assume the feminine role, marry and produce children. Prior to knowledge that biopsy of the gonads revealed testicular tissue, she stated that she would be unhappy if informed that she were male rather than female.

The assay of urinary hormones gave a nearly typical female picture (table 1). Estrogens were present in considerable amount; tests with extracts from 300 cc. of urine gave strongly positive reactions in castrated rats. Considering the imperfection of methods employed at the time, it is probable that the total estrogen content was not below that characteristic of urine of normal women. The androgenic hormones were so low that tests on the combs of chicks by local application gave no positive results, either before or after the operation; a liter of urine contained less than an equivalent of 0.1 mg. of testosterone propionate. However, the presence of small amounts of male sex hormones was indicated by the considerable size and a good histological development of the epididymes. Apparently, enough androgens were released by the testes to stimulate these directly attached and probably most highly reactive organs, while the prostates, rudiments of which almost certainly must be present, remained too small for identification. We have no way of deciding whether the penis developed completely independent of hormonal stimulation. Tannate precipitates were negative for gonadotropins, at the level of one liter.

When, a month later, the individual returned to the hospital with unchanged attitude, it was decided to remove penis and gonads and attempt the construction of an artificial vagina with flaps secured from the scrotal skin. This was done, but the epithelial grafts did not take in the prepared cavity, which was allowed to close after discharge from the hospital. As expected, the operation produced, endocrinologically, the castration effect. The estrogenic hormone disappeared from the urine, while the gonadotropic hormone rose within three weeks to more than 10 R.U. per liter. At an examination 3½ years later, 100 R.U. were found per liter (table 1). Before leaving the hospital, *patient 1* began having fairly severe hot flashes with sweating. Two months after the operation, she had several of these flashes a day. Estrogen preparations were prescribed which gave complete relief. Before the operation, the breasts had been

TABLE 1. PATIENT 1, HORMONES PER LITER OF URINE

Time	Gonadotropin, R.U.	Estrogen, R.U.	Androgen chick U
1 month preoperatively	Below 1	Above 4	Below 1
Operative removal of both testes			
4 days postoperatively		Below 1	Below 1
7 days postoperatively	2		Below 1
14 days postoperatively	6		Below 1
18 days postoperatively	6		
21 days postoperatively	10	Below 1	
3½ years postoperatively	100		

turgent; the individual even reported that they "swell" and "feel tingling" at monthly intervals. At the first examination, the left breast was slightly tender. After the operation, they became rather flabby (fig. 1, 3). The patient gained considerably in weight, which, however, may be due to concurrent change in living conditions. (The patient's weight changed from 121 lb. at the time of the operation to 129½ lb. two and one-half months later.)

Direct questioning did not give a very clear picture of the change in sexual desire of this patient. As previously mentioned, both 'sisters' felt and behaved like normal women; they had their 'boy friends,' were married and wished to be married again. While *patient 1* was in the hospital recovering from laparotomy and appendectomy, she was visited by a boy friend of whom the attendant doctor says: "He seems to be a healthy, normal male of average intelligence." About this visit, the same doctor left the following report: "The two of them seem to be attracted to each other. They hold hands and whisper back and forth as any two normal lovers would." Six weeks after the second operation, the individual estimated that her sexual interests were reduced by one-half.

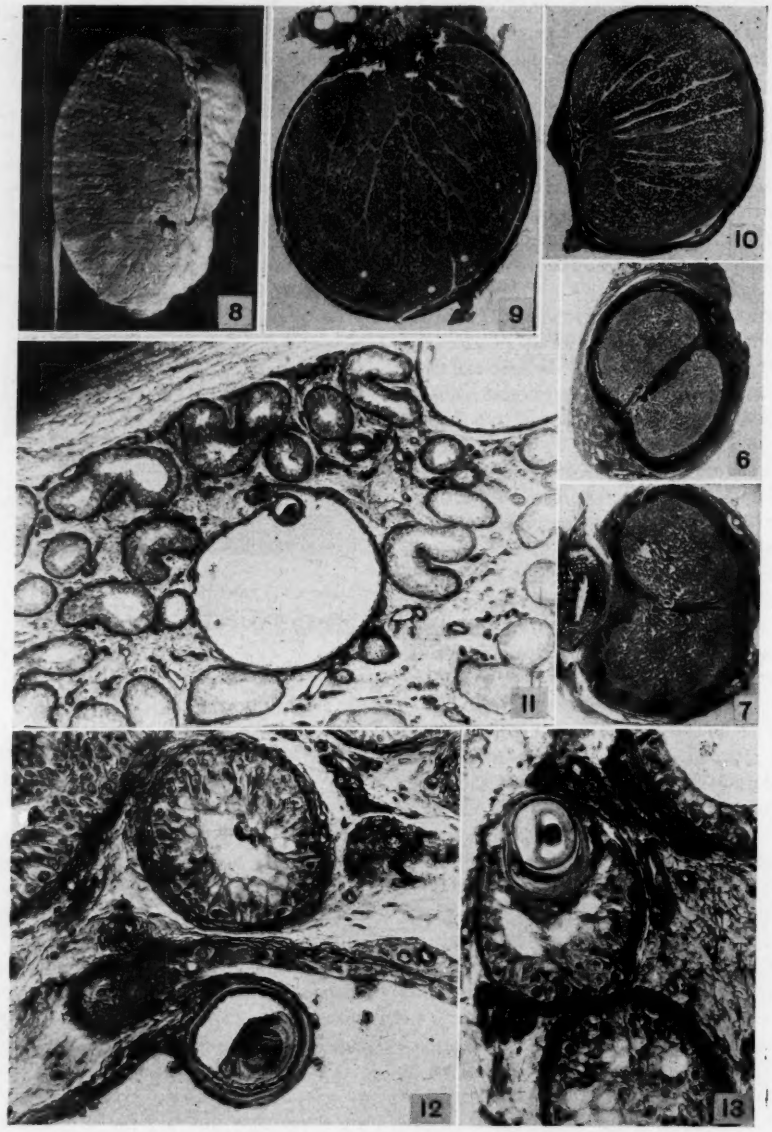

Fig. 6. Cross-secton through penis of *patient 1*. ×2. Fig. 7. Cross-section through penis of a normal man. ×2.

Fig. 8. Half of longitudinally split right testis, with attached epididymis of *patient 1;* natural size. Fig. 9. Cross-section through left testis of *patient 1*. ×2. Note 8 tubular cysts near the surface. Fig. 10. Cross-section through normal testis of a young man. ×2

Fig. 11. Part of a cross-section through testis of *patient 1*. The seminal tubules are mostly sterile or near sterile. In the center is a large tubular cyst. ×25.

Fig. 12. Detail from same section as fig. 11 showing the glandular development of sustentacular cells in a seminal tubule and the egg-like body in a tubular cyst. ×85. Fig. 13. Earlier stage of tubular cyst with small central cavity. Cumulus-like arrangement of sustentacular cells around the egg-like body; a few spermatocytes and spermatogonia in the opposite wall. ×85.

This statement is based on the fact that the presence of the boy friend no longer "bothers" her as it used to. This admission gains weight in view of the then intended—and later effected—second marriage. At the present time, this patient is happily married and refuses to submit to another operation for vaginal manufacture. Her husband, who is comfortably situated financially, is somewhat older than she. Coitus is performed, apparently to the husband's satisfaction, between the perineum and the upper and inner aspects of the closed thighs.

The tissues removed at the time of the operation were studied microscopically. At the present, only a summary account of the findings will be made. Cross sections through the penis (fig. 6) show the considerable size of the corpora cavernosa and absence of the urethra (comp. fig. 7).

The testes were excised together with the epididymes and some adhering tissues (fig. 8). In this condition, the left one weighed 29, the right one 49 gm. Since these testes were unmistakably the source of the estrogens produced during the preoperative period, a thorough search was made for eventual ovarian tissues. They were sliced in discs, and several thousand sections were cut, stained and studied microscopically, but no vestige of ovarian cortex was found. However, the glands are of a remarkable structure (fig. 9–13). Most of the seminal tubules have a smaller diameter than normal, which is due to the relatively low number of germ cells. Spermatogonia are present in most seminal tubules, and some of them are found undergoing mitotic division. Primary spermatocytes are rather rare and completely absent from many tubules. Some develop up to the metaphase of the first maturation division. Secondary spermatocytes or any further advanced spermatogenic stages are found but very exceptionally in these operative specimens, although it is an interesting fact that biopsy samples, taken one month earlier, had contained a few abnormal spermatozoa.

Since the testes were descended and suspended in scrotal sacs of normal dimensions, failure of completion of spermatogenesis must have been due to other causes than those working in cryptorchidism. The adversity of hereditary constitution and of hormonal conditions are the most likely factors responsible for spermatocyte degeneration.

As previously mentioned, a female basic constitution is indicated by the fact that the hermaphrodites have two normal brothers. Cytological study gives no indication of the presence of a pair of XY chromosomes. While admittedly, the analysis of human chromosomes offers considerable difficulties, it is significant that Feulgen-stained primary spermatocytes contain no pycnotic elements that could be interpreted as sex chromosomes. The hermaphrodite which recently was studied by Severinghaus (2) obviously belongs to the opposite sex-class.

The constitutional femaleness is probably the reason for the prevalence of estrogens noted in the hormonal output of the sex glands. The microscopical examination shows that the seminal tubules contain an abundance of sustentacular cells of Sertoli. Generally, they are of healthy appearance, and present the aspect of highly active secretory cells (fig. 12, 13). Distinctly, the most unusual feature of these testes is the presence of thousands of follicle-like vesicles in many seminal tubules, mainly within a zone near the distal surface of the testis (fig. 9, 11). Early stages show a slightly inflated tubular segment containing a cell, probably a germ cell with nucleus, that assumes in the cyst a position like that of the ovocyte in an ovarian follicle. This cell is encased in an envelope consisting of almost homogeneous albumen and resembling, except for its excessive thickness, the zona pellucida of the normal egg. The sustentacular cells appear in the rôle of the granulosa. In young vesicles (fig. 13), they are large, and form a hillock around the egg-like cell resembling the cumulus in the graafian follicle. In the largest vesicles, they flatten, slough off and degenerate while floating in the cyst-like lumen (fig. 11, 12). The wall of the seminal tubule, together with some attached interstitial cells, corresponds to the follicular theca, although giving a rather incomplete imitation. The parallelism of these features must be emphasized, because it offers the only histological clue as to the possible source of the female sex hormones. About the morphological homology of ovarian granulosa and testicular sustentacular cells, there remains little doubt, both arising from the follicle cells of the primordial gonia. The signs of high secretory activity indicate that sustentatcular cells were the producers of the considerable amounts of estrogenic substances noted in this patient previous to the operation.

Clusters of interstitial cells of Leydig are present, though they are small and do not give the impression of much activity.

Description of Patient 2

Four years after *patient 1* was seen, there appeared a young woman at the University Hospitals complaining of "failure to menstruate." Despite the difference in married names, she was soon recognized as belonging to the same family. *Patient 2* was not as evasive and secretive as her 'sister,' although her confidence was not gained until gratitude for the successful manufacture of a functional vagina overcame her diffidence. It was from *patient 2* that the family history was obtained. Both of these individuals recognized the bizarre nature of their deformities and, for this reason, were antagonistic to any suggestion

of direct inquiry among relatives. *Patient 2* consulted her home physician who removed the external genitalia and discarded the gonads. We did not, therefore, have an opportunity in this case for histological and hormonological studies. However, the physician, as well as the patient, assured us, after viewing photographs of the genitalia of *patient 1*, that those of *patient 2* were similar in appearance.

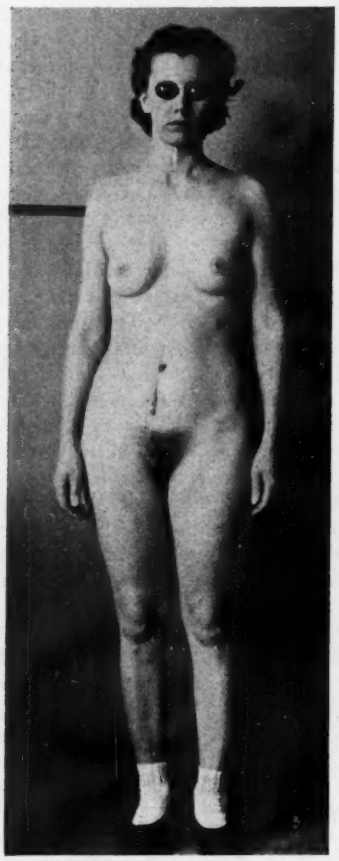

Fig. 14. PATIENT 2, one year after removal of external genital organs.

On examination of *patient 2*, the external body conformation was that of a female (fig. 14). The extremities were not so muscular and therefore slightly more feminine in appearance than those of *patient 1*. There was no facial hair, the voice was feminine and the pubic hair presented the feminine type of escutcheon. The hips were almost as wide as the shoulders, and a roentgenogram revealed a quite typical female bony pelvis (fig. 15). The perineum was scarred, but two small folds resembling nymphae were present. The urethral meatus was directly in front of the symphysis, having been drawn upward by scar tissue. The base of the incompletely removed penis provided clear evidence that this organ originally was of equal size as in *patient 1*. There was no evidence of a prostate gland on rectal examination. The family physician who, at the time of the first operation, had performed a laparotomy with appendectomy reports that no feminine internal genitalia were detectable. Complete absence of abdominal sex glands was definitely ascertained by our hormone tests which revealed the typical castrate condition. Urine samples collected one year after the operation contained 20 R.U. of gonadotropic hormone per liter.

Having tried one marriage, *patient 2* conceded that 'she' wanted to be married again, provided we could

Fig. 15. Pelvis of *patient 2*.

make her a vagina. This procedure was successfully accomplished by removing a one-piece, partial-thickness graft from the abdominal wall with the Padgett dermatome and supporting it with a suitable obturator in a cavity dissected between rectum and bladder.

Four months after this operation, the patient returned for observation, having been married for one month. The artificial vagina readily admitted two fingers for a distance of 9 cm. The 'mucosa' was thrown into folds closely resembling the rugae of a normal vagina, but there was little moisture present.

She claimed to enjoy coitus, experience definite sexual sensation, admitted that orgasm was lacking, but assented that she could hardly expect more. Most of the time artificial lubrication was necessary for intercourse. Overhearing a chance remark that the vagina was not as long as at the time of discharge from the hospital, she became a trifle indignant and stated that under sexual excitement, it lengthened and enlarged in diameter. Her husband is perfectly

satisfied with the vagina. She volunteered the information that she had gained weight and felt better physically than she had for years. Perhaps this sense of physical well-being represents a reflection of an improved mental state, since she no longer has any sense of essential difference from other women.

DISCUSSION

The case of these hermaphrodite 'sisters' becomes of particular interest because there remains little doubt that basically they are of the female sex, in spite of nearly complete male sex organs. They differ from numerous cases of 'male pseudohermaphrodism' and hypospadias in the complete absence of male puberal sex characters. The general proportions of the body of the first patient were prevailingly female, although distinctly shifted in the eunuchoid direction. Those of the second were nearer the female type. This raises the question of the factors determining skeletal growth. Roessle (3), reporting on a 37-year-old congenitally agonadal woman, points out that the pelvis is not of the mature female, but of juvenile or neutral type. Therefore, the female skeletal traits observed in our patients can be considered as indications of hormonal, rather than of immediately genetical, conditions.

On the other hand, reports on individuals born without gonads agree in that the genital ducts are sexually differentiated. This suggests genetical (chromosomal) determination of prepuberal somatic sex characters in man and independence of their early embryological differentiation from gonadal factors. However, the cases of baby girls with adrenal hypertrophy prove that abnormal hormonal conditions may interfere and induce deviations from the normal course of self-differentiation. There are no indications, in our two patients, of adrenal or other endocrine abnormalities. The problem of primary sex differentiation and the prenatal development of the genital ducts of the two cases remains therefore an unsolved problem. The assumption that the two hermaphrodites were basically of female sex merely expresses the conviction that they take the place of the expected female offspring in the family. Yet to all appearances, their hereditary constitution deviates from that of normal females. This genic variation may be the immediate and only cause for the peculiar hermaphrodite type of the early course of sexual differentiation, but the possibility of hormonal interference through the placenta must also be left open.

There appears still another side to this case, in fact a most provoking aspect, suggesting possibilities of far-reaching implications. Assuming the described two individuals, partially sex-reversed females, had been declared, legally, as of the male sex; then their inclinations and instincts obviously would mark them as homosexuals. Now we have to take into consideration the fact that many 'pseudohermaphrodites' have been described which differ from our two patients only in various degrees of development of puberal male sex characters, change of voice and growth of hair. Therefore, the question arises as to what extent homosexuality may rest on sex reversal. That a large proportion of homosexuals is of a purely environmental type is clearly brought out by studies like the most recent one by Henry (4). However, indications of the existence of a congenital and probably hereditary type are numerous. Assuming that a certain number of homosexuals do arise by sex reversal, one must expect the occurrence of corresponding deviations from the normal sex ratio within their families. Intrauterine transformation of female fetuses should increase the male index and transformation of male fetuses should increase the female index. Of foremost interest in this connection is a statistical analysis, by Lang (5, 6), of the families of about 4,000 male homosexuals with police records. His material became available through the circumstance that in Germany, homosexuality among men has been made a criminal offense by laws adopted in 1871. From Lang's data, it appears that: *a*). Among brothers and sisters of homosexuals, the sex proportion is abnormally high and in favor of the male sex (2,078 brothers, 1,685 sisters; ratio 123:100). *b*). Among paternal half-brothers and half-sisters, the sex ratio is even higher (153 half-brothers, 113 half-sisters; ratio 135:100). *c*). Corresponding maternal half-brothers and sisters show an excess in the female sex (210 half-brothers, 234 half-sisters; ratio 90:100). *d*). Children of married homosexual men show the normal sex distribution (143 sons, 136 daughters; ratio 105:100).

Barring the possibility of errors due to small numbers or inadvertent selection, both improbable in the case of this apparently very conscientious work, Lang's data lend themselves for interpretation as follows. Points *a* and *b* indicate that the fathers of some homosexual 'men' are carriers of a gene which, if transmitted to daughters, causes female-to-male sex reversal. Their sex-reversed offspring are potential homosexuals and contribute largely to this group. In an older study, Weil (7) reports that homosexual men as a group show body proportions which deviate from the normal partly in the female (large pelvic diameter) and partly in the eunuchoid direction (long arms and legs). In conjunction with our own observations, this may be interpreted as supporting the thesis of sex reversal as a source of homosexuality.

Point *d* may be taken as evidence that only 'environmental' homosexuals are fertile and capable of reproduction. They produce, as one would expect, an offspring of normal sex proportion. The low average number of children (1 per couple) indicates

widespread sterility. It may be due to total sterility of the hereditary (sex-reversed) group of homosexuals.

Point c requires no special discussion in this paper. It may indicate that some homosexuals are men partially feminized through maternal hormonal influences, as described in an earlier analysis (1) of cases reported by various authors.

On the basis of the data so far available, one still hesitates to make any definite statements concerning frequency of sex reversal in the human race. We had become accustomed to look at human sex determination as a solved problem, as a toss-up between X and Y chromosomes. Deviations of sex ratio, and of morphological and endocrine physiology, as well as of behavior, were only considered as oddities. Now as matters of sex are no longer shrouded with deep secrecy, we begin to realize that aberrations due to modifying genes and special hormonal conditions are much more prevalent than ever suspected. Many of them appear in set patterns and with a surprising regularity. While this may not be yet the time to express opinions about the relationship of sex reversal to certain sex abnormalities prominently affecting human society, it certainly seems timely to start systematic and comprehensive studies in this field in which, so far, little else than collections of case histories has been produced.

SUMMARY

1. Two remarkably similar cases of hermaphrodism are described with prevalence of maleness in the prepuberal and of femaleness in the puberal sex characters. The mental attitude was distinctly of female orientation.

2. Since the two are siblings and have two normal brothers, it is assumed that they are basically of female sex. Chromosome studies support this interpretation.

3. As most likely causes of the deviations, appear either a change in sex-determining genes or special hormonal conditions during pregnancy.

4. Evidence is presented supporting the contention that the sustentacular cells of the seminal tubules were the producers of the female sex hormones which predominated in the hermaphrodites prior to castration.

5. After operations involving castration and some plastic surgery, both individuals obviously were satisfied in their rôles as married women.

6. The possible importance of the cases for the interpretation of sex reversal and homosexuality in man are discussed.

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Monomethyl Ether of Stilbestrol and Menopausal Syndrome

[Stilbestrol Monomethyl Ether]

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Many natural and synthetic compounds are estrogenic, but until recently only the natural compounds have been used clinically. Diethyl stilbestrol represents the first synthetic compound of acceptable clinical value. Since it is a well-known fact that the derivatives of a compound may possess properties enhancing its clinical uses over that of the original, many derivatives of stilbestrol have been studied by Geschickter and Byrnes (1), and by Dodds, Lawson and Noble (2). It has been found that increasing the length of the side chain of stilbestrol decreases the potency, and esterification with aliphatic acids decreases potency but gives a more prolonged estrus. Sondern, Sealey and Kartsonis (3) and Geschickter and Byrnes (1) have studied the estrogenic effects of dimethyl, diethyl, and dipropyl ethers of stilbestrol giving the ratio of activity as 1:5:10:33. Geschickter and Byrnes (1) have found that the monomethyl ether was as potent as diethylstilbestrol and more potent than estrone. In addition to their animal experimental work they evaluated the clinical effect of monomethyl ether in 19 cases of menopausal syndrome. The results compare favorably with those from diethylstilbestrol. They claim that side reactions, namely, nausea and vomiting, were not as marked.

Table 1 shows the data on 36 cases of menopausal syndrome treated with monomethyl ether of stilbestrol. A detailed history in the examination of each case is not given as this is not essential in the clinical evaluation of the results obtained. The cases are classified as natural, surgical and radiation menopause with sub-classifications of mild, moderate and marked.

There were 25 cases of naturally occurring menopause, of which 3 derived no clinical benefit, 4 had fair, and 18 showed good to excellent results. Of these 17 had none of the side reactions noted above, 8 had slight to moderate reactions, and in only one case was it necessary to discontinue the chemical because of side effects. One patient was willing to endure the reactions for the subsequent relief she received. After the third monthly dose of 25 mg. intramuscularly she developed a tolerance to the chemical so far as side reactions were concerned, without any loss of relief of menopausal symptoms and is now taking one mg. per day orally with practically no discomfort. One case had slight nausea with oral administration and none when the substance was given intramuscularly.

There were 7 cases of surgical menopause, 1 of which failed to respond to therapy, 1 responded poorly, 1 fairly, and the remaining 5 showed good results. Only 2 cases in this group had side reactions, and some patients claimed that the clinical effects were as good as with diethylstilbestrol, and better than some natural estrogens.

There were 4 cases of radiation menopause, in 1 of which the clinical effects were not as good as with diethylstilbestrol, while in the other 3 good results were obtained.

Considering the total number of 36 cases, 89 per cent derived clinical benefit and 11 per cent showed no response to treatment. Those not responding to monomethyl ether of stilbestrol did get relief with some one of the natural estrogens. Many of the 89 per cent had been treated previously with diethylstilbestrol and claimed as good and in some instances better results. One patient, treated with every known estrogen claimed better results with monomethyl ether of stilbestrol. Of the 36 cases, 11 (30%) complained of side reactions, though some of these acquired a tolerance for the chemical.

The general method of treatment was to give 0.5 to 1 mg. daily by mouth, or from 5 to 25 mg. monthly by injection, depending upon the clinical response. In some patients 10 mg. monthly in one injection sufficed; others required 25 mg. The doses necessary for the individual were arrived at empirically. Generally 1 mg. per day orally or 25 mg. a month intramuscularly seemed to suffice.

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TABLE 1. RESULTS OF THERAPY WITH MONOMETHYL ETHER OF STILBESTROL

Case; Age, yr.	Dose, Mg., Route	Interval	Results	Side Reactions	Number Months Treated	Remarks
Natural type of Menopause; a) mild symptoms						
1, 37	1 Oral	Daily	Excellent	Nausea	2	Symptoms disappeared after weeks
2, 54	1 Oral	Daily	Excellent	None	1	
3, 44	10–20 Oral	Monthly	Good	None	2	
4, 45	25 Injection	Monthly	Poor	Moderate	10	Estradiol better
5, 31	1 Oral	Daily	Good	None	3	Menstrual migraine
b), Moderate symptoms						
10, 51	20 Injection	Monthly	Good	Slight	4	
11, 33	20 Injection	Monthly	Fair	None	1	
12, 44	10 Injection	Monthly	Fair	None	3	
13, 45	10 Injection	Monthly	Fair	Moderate	3	
14, 48	10 Injection	Monthly	Good	None	7	
	1 Oral	Daily	None	Slight		
15, 50	25 Injection	Monthly	Good	None	7	
16, 41	10 Injection	Monthly	Good	None	9	
17, 47	25 Injection	Every 6 weeks	Good	None	7	
18, 51	25 Injection	Monthly	Good	None	8	
	1¼ Oral	Daily	Good	None		
19, 44	25 Injection	Monthly	Good	None	3	
20, 54	15 Injection	Monthly	Fair	Moderate	6	Poor case
	1 Oral	Daily	Fair	Moderate		
21, 46	25 Injection	Every 6 weeks	Good	None	8	
	1 Oral	Daily	Good	None		
22, 52	25 Injection	Monthly	Good	None	4	
c), Marked symptoms						
30, 48	5–10 Injection	Bimonthly	None	None	3	
31, 52	½ Oral	Daily	None	Marked headache	½	Could not tolerate diethyl stilbestrol
32, 46	1 Oral	Daily	Good	None	4	
	50 Injection	Monthly	Good	None		
33, 51	10 Injection	Monthly	Good	None	12	
34, 47	25 Injection	Monthly	Excellent	Nausea 1st 3 injections	8	Willing to tolerate for relief
35, 46	25 Injection	Monthly	Good	None	4	
36, 50	50 Injection	Monthly	Good	None	5	Better than estradiol benzoate
Surgical Type of Menopause; a) moderate symptoms						
40, 53	10 Injection	Every 3 weeks	Good	None	5	
	1 Oral	Daily	Poor	None		
41, 46	25 Injection	Monthly	Good	None	3	Results comparable with those with diethylstilbestrol
b) Marked symptoms						
50, 33	25 Injection	Monthly	Good	None	5	Treated with every available estrogen, monomethyl ether of stilbestrol better.
51, 53	5–10 Injection	Weekly	None	Moderate	1	
52, 51	20 Injection	Monthly	Fair	None	1	No relief with 5 mg. orally
53, 28	25 Injection	Monthly	Good	None	4	Endometritis
	1 Oral	Daily	Good	None		
54, 38	20 Injection	Monthly	Good	Slight	6	Better than estrone
Radiation Type of Menopause; a) moderate symptoms						
60, 50	1 Oral	Daily	Good	Slight nausea	2	Diethylstilbestrol better
61, 50	1–2 Oral	Daily	Fair	None	1	

TABLE 1. RESULTS OF THERAPY WITH MONOMETHYL ETHER OF STILBESTROL

Case: Age, yr.	Dose, Mg.,	Route	Interval	Results	Side Reactions	Number Months Treated	Remarks
b) Marked symptoms							
70, 41	1	Oral	Daily	Good	None	4	Better than diethylstilbestrol
71, 46	25	Injection	Monthly	Good	None	5	

SUMMARY

A series of 36 cases was treated with monomethyl ether of stilbestrol and 89 per cent of these responded favorably, while 11 per cent received no benefit from treatment. Many of those at first showing side reactions acquired a tolerance for the chemical without loss of clinical effects, and in only one case was it necessary to discontinue the treatment entirely. These results are encouraging and certainly compare favorably with results obtained with other forms of estrogen therapy.

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Clinical Use of Methylstilbestrol[1,2]

[Methylstilbestrol]

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SINCE THE ESTROGENIC PROPERTIES of diethylstilbestrol were first described by Dodds and associates (1) in 1938, extensive clinical work has been done to determine the estrogenic potencies and possible toxic effects of this drug (2–6). Its use by a number of investigators in various clinics has demonstrated pronounced estrogenic potency and mild toxicity, the latter consisting of nausea and occasional vomiting in a small percentage of cases. Various laboratory procedures used to determine possible specific organic damage from the drug have been negative in the hands of most investigators (2, 7).

Aside from the diethyl group attached to the stilbestrol base, a number of other substituent groups have been used to formulate other compounds which might have estrogenic potency.

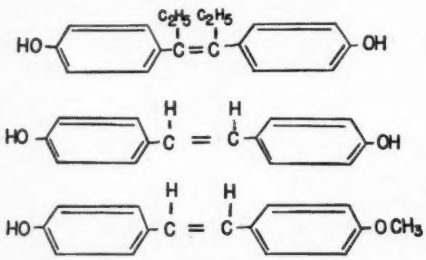

Fig. 1. TWO STILBESTROL COMPOUNDS WHICH HAVE PROVEN ESTROGENIC POTENCY SHOWN WITH THE BASIC STILBESTROL FORMULA

Geschickter and Byrnes (8) assayed a large number of these different stilbestrol compounds on animals, finding varying estrogenic potency; and clinically assayed the monomethyl ether of stilbestrol on 49 cases of varying types necessitating estrogen therapy. The conclusions from the latter work were that the monomethyl ether of stilbestrol was a highly effective estrogen with less toxicity, as observed from clinical symptoms, than diethylstilbestrol. When it was used intramuscularly, in oily solution, these writers were under the impression that the estrogenic effect was more prolonged.

The present report concerns the clinical use of the monomethyl ether of stilbestrol, commonly known as methylstilbestrol, on 25 cases necessitating estrogen therapy. Eighteen cases were treated for menopause symptoms, 3 for amenorrhea and 4 for dysmenorrhea.

For the most part, the drug was administered by mouth in dosages varying from 2 mg. in 40 days to 390 mg. in 13 days. Occasional cases were treated by intramuscular injection. Toxic effects of methylstilbestrol occurred in 4 cases, consisted of nausea and vomiting only, but were not severe enough to necessitate cessation of therapy in any case. The occurrence of toxic manifestations was equally divided between oral and intramuscular administration and their interpretation was entirely on a clinical basis. Since blood studies and liver and kidney function tests had been made previously on cases receiving diethylstilbestrol (2) it was not considered necessary to repeat them in this series.

Of the menopause cases, 5 were surgical, 4 followed radiotherapy and 9 were physiological.

These were members of a larger menopause group, all of whom had originally received small doses of phenobarbital; and the 18 treated with methylstilbestrol were the members of this group who had not been relieved by the former therapy. Nine of these patients received complete relief from this particular

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[2] We are indebted to Dr. Franz C. Schmelkes of Wallace and Tiernan Products, Inc., Belleville, N. J., for a generous supply of the methylstilbestrol.

TABLE 1. RESULTS OF TREATMENT OF PATIENTS WITH METHYLSTILBESTROL

Case Number	Age, years	Diagnosis	Treatment	Side Effects	Results
1	52	Menopause	2.5 mg. daily for 14 days 2.5 mg. every other day for 28 days	None	Good
2	41	Menopause	1.0 mg. daily for 34 days	None	Fair
3	51	Menopause	1 mg. intramuscularly 1 mg. daily for 52 days	Moderately severe nausea, slight vomiting	Poor
4	53	Menopause	5 mg. intramuscularly, q. 3–4 weeks	None	Good
5	39	Menopause	1 mg. intramuscularly per week	Slight nausea and vomiting after 3rd injection	Fair
6	43	Menopause	0.5 mg. 4 times a week for 4 weeks	None	Good
7	48	Menopause	0.5 mg. daily for 16 days 0.1 mg. every other day for 26 days	None	Good
8	49	Menopause	1 mg. daily for 7 days 0.5 mg. daily for 21 days	None	Good
9	50	Menopause	2.5 mg. daily for 21 days 2.5 mg. daily for 21 days	None	Good
10	49	Menopause	1 mg. daily for 14 days	None	Poor
11	50	Menopause	1 mg. intramuscularly for 9 days	None	Poor
12	34	Menopause	0.5 mg. daily for 28 days 0.5 mg. daily for 42 days	None	Fair
13	41	Menopause	0.1 mg. daily for 14 days 0.1 mg. every other day for 21 days	None	Good
14	52	Menopause	1 mg. daily for 30 days	None	Fair
15	48	Menopause	0.5 mg. daily for 28 days 0.5 mg. every 3rd day for 60 days	Slight nausea and abdominal pain	Good
16	42	Menopause	5 mg. intramuscularly q. 4 weeks for 1 year	None	Good
17	38	Menopause	1 mg. daily for 13 days	None	Fair
18	46	Menopause	0.1 mg. every other day for 40 days	None	Fair
19	34	Amenorrhea	0.5 mg. daily for 85 days	None	Fair
20	24	Amenorrhea	2.5 mg. daily for 20 days; total, 50 mg.	None	Withdrawal bleeding 2 days after cessation of treatment
21	20	Amenorrhea	5 courses of 30 mg. daily for 13 days; total, 390 mg. per course	None	Withdrawal bleeding following each course
22	35	Dysmenorrhea	5 mg. daily for 21 days 2.5 mg. daily for 18 days	None	Excellent
23	22	Dysmenorrhea	2.5 mg. daily for 25 days 2.5 mg. daily for 10 days 2.5 mg. daily for 21 days	Slight nausea and lassitude	Excellent
24	14	Dysmenorrhea	30 mg. daily for 2 days premenstrually	None	Excellent
25	29	Dysmenorrhea	2.5 mg. daily for 21 days	None	Excellent

estrogen, 6 were improved and 3 unimproved (table 1). The amount of dosage could not be correlated with relief of symptoms.

It will be noticed from table 1 that *case* 3 developed nausea and vomiting following intramuscular injection but not following peroral therapy, and that

case 4 was relieved of symptoms for as long as 4 weeks by a single injection of 5 mg. intramuscularly and had no toxic manifestations.

Methylstilbestrol was administered to 3 cases of secondary amenorrhea.

One case ceased menstruating suddenly at the age of 34 and complete investigation of the patient s physical status (including basal metabolic rate, roentgenogram of the sella turcica and blood studies) revealed no abnormalities. Very thin atrophic endometrium was found at curettage. Over subsequent months massive estrogen and progesterone dosage, both separately and combined, produced no withdrawal bleeding, nor developed any endometrium. As a further trial, the patient was given small doses of this estrogen (0.5 mg. of methylstilbestrol) daily over a period of 3 months, during which time she had two periods of light bleeding lasting 3 days each, but there was still no evidence of endometrial proliferation on endometrial biopsy.

The second case of amenorrhea may well be considered a bad diagnostic error. A 24-year-old girl with a two-year history of amenorrhea was greatly disturbed concerning her failure to menstruate. The physical examination and laboratory workup, including basal metabolic rate, were negative. She was therefore given 2.5 mg. of methylstilbestrol daily over a period of 20 days and withdrawal bleeding occurred two days after cessation of treatment. At this time it was noticed that she had not had a pituitary roentgenogram, usually a routine procedure before starting therapy; and subsequent x-ray disclosed a large sellar tumor which was later diagnosed as a chromophobe adenoma of the pituitary. Further questioning of the patient revealed that she had been having 'eye trouble' for over 6 months consisting of frequent diplopia for which she was being treated elsewhere, and that she suffered from frequent headaches. She did not consider these symptoms of sufficient importance to mention them, which is, however, no excuse for our not having asked about them when her history was taken. Since these symptoms, plus the amenorrhea, were of comparatively long standing, it was not thought that the therapy was a contributory factor in the pituitary tumor formation. This is a case in which an important diagnostic step had been neglected and it is presented in considerable detail to impress not only upon others, but upon ourselves, the importance of pituitary roentgenograms in all cases of amenorrhea.

The third case of amenorrhea complained also of pronounced hirsutism. Complete preliminary investigation proved negative and laparotomy disclosed no adrenal abnormalities but large ovaries filled with multiple small follicles, none of which, however, had grown to maturity. Several patients of this type with similar pathological findings will be a subject for future report. In a later effort to check the hirsutism, however, this patient was given 30 mg. of methylstilbestrol daily in courses lasting 21 days and she had repeated periods of withdrawal bleeding.

The above three cases are presented here not so much because of their peculiar physiological abnormalities but more as evidence of the estrogenic effects of methylstilbestrol.

Of a large group of dysmenorrhea cases receiving estrogen therapy of various types, 4 were treated with comparatively large doses of methylstilbestrol.

In 3 cases (*22*, *23* and *25*, table 1) the method of treatment was to give daily estrogen therapy throughout the first 21 days of the cycle in sufficient quantity to prevent ovulation, the resultant failure of progesterone secretion caused thereby producing a relief of dysmenorrhea (9). Complete relief of symptoms occurred in these 3 cases.

One patient suffering from dysmenorrhea was given 30 mg. of methylstilbestrol daily for 2 days just before the onset of menstruation and she also was completely relieved of symptoms.

These 4 cases indicate subjectively, at least, the estrogenic potency of methylstilbestrol.

One patient suffered from slight nausea at the beginning of treatment.

SUMMARY

The monomethyl ether of stilbestrol, commonly known as methylstilbestrol was administered in varying dosage to 25 cases necessitating estrogen therapy.

Eighteen menopause cases were treated. Nine were completely relieved, 6 were improved and 3 unimproved.

Withdrawal bleeding was produced in 3 cases of amenorrhea due to various abnormalities.

Four cases of dysmenorrhea were completely relieved of symptoms.

Transitory nausea and vomiting occurred in 4 of the 25 cases.

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Estrogenic Content of Cirrhotic Livers

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IN 1934 ZONDEK (1) reported experiments indicating that the liver was capable of inactivating estrogens. This has been confirmed by other authors using a variety of methods. It would, therefore, seem logical to assume that the function of diseased livers might be impaired in this respect and that such livers might contain demonstrable estrogens.

While this piece of work was being completed, a paper appeared by Glass et al. (2). These authors, arguing along similar lines studied the estrogenic content of urines from 14 cases with chronic liver disease. They found an increased amount of estrogens in every case. In 8 cases they assayed both the free and combined estrogens and found that the hormones occurred entirely in the free form, not in the combined form in which they are normally excreted. The authors concluded that their data indicated failure of cirrhotic livers to inactivate estrogens.

In the present study, the estrogenic content of liver tissue was determined.

MATERIAL AND METHODS

Our material consists of livers obtained at autopsy from the pathological service here and from the Medical Examiner's service. In addition to the hormone studies, histological examinations were made of every liver.

The estrogens were extracted as follows. Fifty or 100-gram lots of liver were finely ground with a meat chopper, covered with 5 times their volume of acetone and allowed to stand for 24 hours at room temperature. The acetone was poured off and a fresh lot added to the tissue. After another 24 hours at room temperature, the second lot of acetone was filtered off and the tissue residue placed in the incubator for 2 to 3 hours in order to evaporate the acetone. The tissue was then covered with 5 times its volume of ether and allowed to stand at room temperature for 5 to 6 hours. The ether was then decanted and fresh ether added. The first lot of ether was added to the residue obtained by evaporating the combined lots of acetone. After 18 to 20 hours the second lot of ether was filtered and this ether filtrate was added to the first lot of ether. The combined ethers were then filtered. Since many of the livers contained a large amount of fat, a method had to be adopted which would separate the estrogens from such fats. To do so we employed the method devised by Callow et al. (3). In brief this consists of shaking the ether extracts in a separatory funnel with 2N NaOH, acidfying the alkaline aqueous extract with concentrated HCl, extracting this with ether and finally evaporating the ether with the requisite amount of olive oil. We obtained a yield of approximately 50 per cent of the estrogens present by this method. The oil was tested for its estrogenic content on castrated female mice, primed each time 10 days before use by the injection of 8 I.U. of theelin.[1]

The total number of livers studied was 42. Of these, 23 were from cases of cirrhosis; 21 were of the alcoholic type, 1 was a pigment cirrhosis and 1 a biliary cirrhosis. The remainder consisted of a heterogeneous collection of conditions designed to serve as controls. Some were from normal individuals killed in accidents, others were from patients dying from a variety of diseases other than sepsis or tuberculosis, for we felt that such diseases might introduce a complicating factor.

The results together with certain pertinent data regarding each case are summarized in tables 1 and 2.

COMMENT

It would seem worth while to comment briefly on certain of the data presented in tables 1 and 2 and on some additional data.

Cirrhotic livers. Of the 23 cases of cirrhosis, 15 contained demonstrable estrogens. An attempt was made to correlate the hormonal findings with the

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[1] The theelin was supplied by Parke, Davis & Co., Detroit, Mich.

degree of cirrhosis, the presence or absence of bile stasis and the amounts of lipoid present but no such correlation could be established. Furthermore, the importance of the cirrhosis as a cause of death was considered but this did not appear to be relevant for liver damage due to cirrhosis leading up to the patient's death was as frequent in the positive as in the negative cases.

Noncirrhotic livers. Nine of the 19 noncirrhotic cases contained estrogens. The great majority of the livers in this group were histologically negative and

TABLE 1. CASES IN WHICH ESTROGENS WERE FOUND IN LIVERS

Sex	Age	Estrogens[1]	Liver Pathology	Cause of Death
	yr.			
F	61	55	Cirrhosis	Carcinoma of pancreas
M	59	100	Cirrhosis	Cirrhosis
M	70	80	Cirrhosis	Cerebral hemorrhage
M	84	40	Cirrhosis	Cirrhosis
M	70	80	Cirrhosis	Erysipelas
F	32	73	Cirrhosis	Cirrhosis
F	65	40	Cirrhosis	Cirrhosis
M	64	40	Cirrhosis	Lobar pneumonia
M	66	80	Cirrhosis	Cirrhosis
M	80	80	Cirrhosis	Accident
M	64	133	Cirrhosis	Cirrhosis
M	45	40	Cirrhosis	Cirrhosis
M	62	20	Cirrhosis	Cirrhosis
M	36	40	Cirrhosis	Accident
M	43	133	Cirrhosis	Cirrhosis
F	40	172	Negative	Heart disease
M	70	80	Central necrosis	Bronchiogenic carcinoma
M	89	40	Negative	Pernicious anemia
M	70	40	Negative	Gastric ulcer
M	67	160	Negative	Encephalomalacia
F	59	20	Congestion	Heart disease
F	50	40	Negative	Suicide
M	19	25	Negative	Accident
M	18	35	Negative	Accident

[1] Expressed as castrated mouse units per kg. of wet tissue.

none showed any changes severe enough to interfere with function.

Sex. Nineteen of the positive cases were males and 5 were females. In the cirrhotic group, the livers of which contained estrogens, 13 were males and 2 were females. In the noncirrhotic group with positive hormonal findings, 6 were males and 3 were females. Five of the cirrhotic cases with negative estrogens were males and 3 were females. In the noncirrhotic group which contained no estrogens, 6 were males and 4 were females. In evaluating the significance of sex in this whole series there must be taken into account the fact that males predominated in a ratio of 2.5 to 1; furthermore that of the 23 cases of cirrhosis 18 were males.

Age. The age of the patients was not apparently a factor in explaining the presence or absence of hormones for the series covered a wide range. Two facts seem worthy of note. The first is that the livers of 2 normal males aged 18 and 19 respectively contained estrogens. The second is that the livers of some women past the menopause both cirrhotic and noncirrhotic contained estrogens.

Testicular activity. Tissue from the testicles of 14 of the cases was available for histological study. Ten of these were from the positive cases, 6 from the cirrhotic group. Five of these showed varying degrees of decreased activity while one was normal. Of the noncirrhotic group, 2 were hypoactive and 2 were normal. Of the testes from the cases with negative hormonal findings, 2 in the cirrhotic group were active, 1 was hypoactive. The testes from the one case in the noncirrhotic group with negative estrogens on which tissue was available for study were active. Therefore it would appear that the presence of estrogens in the liver is not dependent on loss or decrease of gonadal activity. Furthermore, it may be mentioned that in no instance was gynecomastia noted either clinically or at postmortem examination.

Time postmortem. It was felt that the time after death that the tissues were examined might have played a rôle in the hormonal findings since it is known that autolysis may have an influence on estro-

TABLE 2. CASES IN WHICH NO ESTROGENS WERE FOUND IN LIVER

Sex	Age	Estrogens[1]	Liver Pathology	Cause of Death
	yr.			
M	43	−66	Cirrhosis	Cirrhosis
M	76	−59	Cirrhosis	Cirrhosis
F	71	−40	Cirrhosis	Hypertension
M	59	−40	Cirrhosis	Cirrhosis
F	33	−60	Cirrhosis	Alcoholism
M	57	−20	Cirrhosis	Heart disease
F	50	−55	Cirrhosis	Cirrhosis
M	68	−40	Cirrhosis and hepatoma	Cirrhosis
F	20	−58	Negative	Glomerulonephritis
F	38	−20	Central necrosis	Bronchiogenic carcinoma
M	24	−40	Negative	Accident
F	33	−40	Negative	Alcoholism
M	26	−40	Central necrosis	Heart disease
F	48	−40	Negative	Cerebral hemorrhage
M	6	−20	Negative	Accident
M	10	−20	Negative	Accident
M	54	−20	Negative	Accident
M	70	−20	Fatty infiltration	Heart disease

[1] Figures indicate C.M.U. per kg. of wet tissue at which tests were negative.

gens. However, no correlation could be found between this factor and the estrogenic content of the livers.

In short, then, our original thesis that cirrhotic livers might contain estrogens was confirmed in part in that the majority of such livers contained estrogens. However, not every case did so. Furthermore, estrogens could be demonstrated in essentially normal livers from both males and females. The explana-

tion of this finding is not clear at the present time. Since we did not employ hydrolysis in extracting the hormones, it would seem probable that they existed in the free rather than in the combined form, our results in this respect agreeing with those of Glass et al. (2).

SUMMARY

1. The livers from 23 cases of cirrhosis were examined for estrogens. Fifteen gave a positive result.

2. Nineteen noncirrhotic livers were similarly studied. Nine contained estrogens.

3. The presence of estrogens could not be accounted for by the degree of cirrhosis, the age, sex or gonadal activity of the patients.

4. The livers of some women past the menopause and of normal young men were found to contain estrogens.

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Excessive Uterine Bleeding: Antigonad Effect of Prolactin

[Pituitary-Ovarian Relationship]

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IN JUNE, 1937, the writer began clinical investigation of the effects of prolactin when administered during phases of excessive uterine bleeding. Thirty-five cases were reported in 1938 (1). During the clinical investigation of the effects of the lactogenic hormone on phases of excessive uterine bleeding, several preparations of prolactin have been used.[1] Information has been received from Lyons (2) that none of these has been pure lactogenic hormone. The prolactin used in the current series however, is sufficiently pure and potent to be used effectively for controlling excessive uterine bleeding, and the following report seems to justify its wider usage for this purpose. In every case in which there was no pathological condition such as fibromyomata, intrauterine papillomata, or persistent thick-walled cysts, the lactogenic hormone therapy was satisfactory. Cessation of excessive bleeding in cases of fibromyomata has been obtained in variable percentages in each series of patients. The majority of patients are improved and several have continued to maintain normal menstrual functions without any surgical procedures for as long as 4 years. Endometrial hyperplasia, when not associated with a persistent cyst or tumor growth, may regress with prolactin and equine gonadotropin therapy.

Goldzieher observed that 'Uterine bleeding which is greater than normal in quantity or which occurs at too short intervals is looked upon as a sign of abnormal ovarian function' (3). Uterine bleeding in the presence of local pathological processes such as polyps, submucous fibroids or malignant tumors of the uterus is not functional in character and consequently cannot be expected to be cured by hormone therapy. There is, however, a hormonal pathogenesis of fibromyomata (4). Many patients who have fibromatous growths, have responded well to prolactin therapy, and maintained normal menstrual function for many months after therapy has been discontinued.

In the presence of persistent follicle cysts it is difficult to control the disturbed physiology and the bleeding with the usual doses of prolactin. Three patients with palpable normal sized ovaries, and with no uterine growths present, continued to bleed excessively in spite of prolactin therapy. Subsequently, at laparotomy at least one follicle cyst was found in each patient.

Careful, complete physical examinations, B.M.R. determinations and endometrial biopsy records are made of each patient, and vaginal smears made during the non-bleeding phases.

One to two hundred international units of prolactin have been given subcutaneously during each day of the bleeding, usually in doses of 100 I.U. Beginning on the second or third day of the following period of menstruation, the hormone may be administered again daily, if the bleeding has been too heavy, and until the bleeding stops. If there is no excessive bleeding during the next menstruation, then equine gonadotropin therapy may be indicated, 2000 I.U. being given on the 9th, 10th, and 11th days of the cycle.

In this second series of reports, prolactin was administered to 56 patients of whom 34 had functional excessive bleeding, and 22 had fibromyomata at the first examination; several of these had various other conditions such as persistent follicle cysts which were diagnosed as surgical cases, because therapy relieved but did not cure the disturbance.

Of the 34 cases of functional excessive bleeding 33 improved with from 300 to 2400 I.U. of the prolactin in 3 to 24 doses for each patient, averaging 800 units per patient. One patient required 6300 I.U. over a total period of 24 months. This patient was 27 years old and had menstruated almost daily for 13 years. Treatment with 3600 I.U. of prolactin during 3 months, followed by 24,000 I.U. of gonadotropin during 4 months, resulted in apparently normal menstrual periods, for 11 months. Bleeding became prolonged again, although not excessive in quantity,

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[1] Acknowledgment for supplies of prolactin are made to: Dr. F. Fenger, Armour Laboratories, Chicago, Ill.; Dr. R. M. Rice, Eli Lilly & Co., Indianapolis, Ind.; Dr. J. P. Schooley, Difco Laboratories, Detroit, Mich.; Dr. M. Gilbert, Schering Corporation, Bloomfield, N. J.

TABLE 1. FUNCTIONAL BLEEDING CASES, NO GONADOTROPIN THERAPY

Name	Age	Duration of Bleeding	B.M.R.	Endometrial Biopsy	Vaginal Smear Before Prolactin[1]	Duration of Prolactin Treatment	Total Dosage of Prolactin	Vaginal Smear After Prolactin	Biopsy After Prolactin; Remarks
Mrs. R.W.	46	21 days, 1st time	+8	Late estrogenic, 23rd day	4+ 23rd day	20 weeks	I.U. 1900	2+ 24th day	4 months after therapy menses ok, scanty
Mrs. J.G.	41	10 days, 1 year	−7		3+ 10th day	5 weeks	500	4+ 25th day	Uterus smaller after prolactin
Mrs. A.B.	49	Irregularly throughout each month, 3½ years	+5	Atrophic, 20th day	2+ 20th day	15 days	800	3+ 28th day	No surgery
Mrs. A.S.	26	21 days, 1st time			3+ 21st day	7 days	400	4+ 11th day	Urticaria after 4th day. No further trouble. Normal periods
Mrs. A.J.	44	7 days, 2× monthly, 3 months	−4	Early estrogenic, 18th day	2+ 18th day	2 days	200	2+ 18th day	Atrophic 18th day
Mrs. R.W.	46	21 days, 1st time	+11	Mild hyperplasia, 22nd day	5+ 21st day	6 weeks	1000	3+ 26th day	Early estrogenic 26th day
Mrs. E.E.	44	2–5 weeks, 4 months	−3	Late estrogenic, 36th day	5+ 36th day	6 days	600	3+ 42nd day	Late estrogenic 42nd day
Mrs. B.G.	49	23 days, 1st time		Early estrogenic, 23rd day	4+ 23rd day	4 days	300	2+ 27th day	Early estrogenic, 26th day
Mrs. L.H.	41	6 days, (48 pads), 1st time			5+ 6th day	4 days	400	2+ 14th day	Menses normal thereafter
Miss R.B.	46	21 days, 1 year	+5	Cystic hyperplasia, 20th day	5+ 20th day	9 weeks	700	4+ 10th day	Only slight improvement; pulmonary carcinoma
Mrs. A.C.	46	Each midmonth, days	+3	Early estrogenic, 10th day	4+ 10th day	14 weeks	1400	2+ 23rd day	Operation for intrauterine fibromyoma 8 years before
Miss E.C.	47	5 weeks continuous, then 2–3 weeks monthly, 10 months	+8	Early estrogenic, 18th day	3+ 14th day	6 weeks	800	2+ 14th day	Occasional scanty bleeding the following year

[1] *Classification of vaginal smears* (5). An effort is made to show a gradual change in the type of the stratified squamous epithelial cells from the basal cells as found during complete absence of estrogen through to the follicular type of cornified cells as may be found during normal ovarian function. 1+. Artificial menopause atrophic type; basal cells, very small round cells with large nuclei, pronounced leucocytosis. 2+. Natural menopause type; less atrophic, larger round cells, though still quite small; transitional phase; less leucocytes; may be with or without mucous. 3+. Represents a comparatively low estrogen level; appearance of larger cells with smaller nuclei; beginning cornification; some small cells still present; few leucocytes. 4+. Larger cells; some cells with pyknotic nuclei. 5+. Represents a premenstrual follicular type of smear. Large cornified cells with pyknotic nuclei; quite clear cytoplasm. 6+. Very large cornified cells, often in clumps; large granules in cellular cytoplasm; nucleus larger, beginning to swell up; some folding of cells apt to be present. 7+. Large cornified cells; granules smaller; nuclei smaller; probably portions of nuclei already broken off; keratinization well advanced; curling of edges of some cells with a variety of shapes. Vaginal smears that are taken for clinical evaluation only, might well be made routinely during the third or the beginning of the fourth week of the cycle. Comparison of findings for the individual patient can be made during the same phase of each cycle.

and further treatment for 6 months with 3700 I.U. of prolactin was required to correct it. The patient received a total of 6300 I.U. of prolactin, at the end of which time she had a 6+ degree of vaginal cornification (5). This case gives evidence of the transitory effects of prolactin and the freedom from danger of abnormal physiological changes.

During a period of 4.5 years more than 700 doses of prolactin, of 100 I.U. each, obtained from the various manufacturers, have been administered to a total of 160 patients. Nine had serum reactions within 20 to 90 minutes; these were manifested as mild generalized urticaria. All were confortable within a few hours following adrenalin chloride therapy. None

TABLE 2. FUNCTIONAL BLEEDING CASES, GONADOTROPINS USED

Name	Age	Duration of Bleeding	B.M.R.	Endometrial Biopsy	Vaginal Smear Before Prolactin	Duration of Prolactin Treatment	Total Dosage of Prolactin	Vaginal Smear After Prolactin	Gonadotropin,[1] Total Dose	Vaginal Smear After Gonadotropin	Biopsy and Comments
							I.U.		I.U.		
Mrs. M.H.	24	Scanty; continuous 6 months	−7	Early estrogenic phase, 24th day	3+ 24th day	12 weeks	1000	3+ 24th day	24,000 4 months	6+ 24th day	Normal periods
Mrs. R.F.	32	6 days 2×month, 2 months	+4	Mild hyperplasia, 14th day	4+ 14th day	11 weeks	1000	3+ 14th day	24,000 4 months	6+ 18th day	Pregnant following month
Mrs. L.Z.	31	8 days, 2×month, 7–8 months	+7	Late estrogenic phase, 24th day	5+ 24th day	10 days	300	5+ 24th day	18,000 3 months	6+ 18th day	Cystic ovary no longer palpable; follicle cyst removed 5 yr. before
Mrs. D.P.	34	14 days, 1st time		Late estrogenic, 14th day	5+ 14th day	2 weeks	600	3+ 18th day	12,000 2 months	6+ 24th day	Menses 3 days a month since treatment
Mrs. R.J.	27	8 days, very heavy, 2 months	−2	Late estrogenic, 19th day	5+ 10th day	1 week	600	3+ 17th day	24,000 4 months	5+ 18th day	Right ovarian follicle cyst. Pelvic adhesions
Mrs. M.H.	24	Spotting continuous 9 weeks; 2–5 week cycles		No biopsy	2+ 8th day	8 weeks	900	2+ 10th day	18,000 3 months	5+ 19th day	Pregnant 5 months later
Mrs. B.A.	20	3 days, 2× month, 9 months		Cystic hyperplasia, 8th day	5+ 8th day	2 weeks	400	3+ 9th day	18,000 3 months	6+ 18th day	
Mrs. C.B.	32	18 days, 1st time	−6	Late estrogenic, 14th day		8 days	500	3+ 24th day	24,000 4 months	5+ 18th day	Pregnant 2 months later
Mrs. J.G.	41	8–15 days, 1 year		Early estrogenic, 12th day	3+ 12th day	4 weeks	500	4+ 18th day	6000 1 month	3+ 18th day	Normal periods
Mrs. L.C.	23	2–3 weeks, 5 months	+2	Late estrogenic, 10th day	4+ 10th day	23 weeks	1400	4+ 24th day	18,000 3 months	4+ 18th day	Normal menstruation
Miss J.B.	18	10 days, 1 year	+6	Early estrogenic, 14th day	5+ 14th day	14 weeks	500	4+ 21st day	24,000 4 months	6+ 18th day	Masculine hirsutes and body; virgin
Mrs. G.G.	49	10 days, 3 months		Early estrogenic, 10th day	2+ 10th day	16 weeks	900	2+ 14th day	6000 1 month	4+ 18th day	Normal flow thereafter
Miss M.A.	26	2 weeks, 3 years	−4	Mild cystic hyperplasia, 20th day	5+ 20th day	13 weeks	1100	3+ 13th day	6000 1 month	4+ 18th day	One ovary out 6 years ago; curettment 3 years ago
Miss M.N.	27	10 days, 9 months	+4	Mild hyperplasia, 10th day	4+ 10th day	1 week	600	3+ 20th day	8000 1 month	5+ 18th day	Normal menses since
Mrs. H.S.	37	5–7 days, 2× month, 5 months	−7	Marked hyperplasia, 7th day	5+ 7th day	7 weeks	400	2+ 21st day	18,000 3 months	5+ 18th day	Normal menses since
Mrs. D.S.	26	10 days, 4 months	−7	Late estrogenic, 18th day	5+ 18th day	9 weeks	1000	4+ 20th day	18,000 3 months	5+ 18th day	Normal menses since
Miss L.N.	23	3 weeks, 4 months	+3	Late estrogenic, 18th day	4+ 23rd day	20 weeks	600	3+ 26th day	10,000 2 months	5+ 18th day	Normal menses since
Mrs. N.W.	35	10 days, 5 months	−6	Early estrogenic, 8th day	5+ 8th day	16 weeks	700	3+ 9th day	18,000 3 months	5+ 18th day	Normal menses since
Mrs. S.M.	27	4 days, 2× month, 2 months	+8	Early estrogenic, 8th day	3+ 8th day	5 months	1200	3+ 23rd day	24,000 4 months	6+ 20th day	Normal menses since
Miss C.G.	27	13 years, almost daily	+8	Mild hyperplasia, day of cycle (?)	5+ Day of cycle (?)	Total of 24 months	6300	2+ 9th day	24,000 4 months	6+ 18th day	Early estrogenic, 9th day
Mrs. C.O.	21	10 days, 1st time	+10	Late estrogenic, 21st day	5+ 21st day	10 days	100	3+ 21st day	12,000 2 months	6+ 18th day	Pregnant 2 months later
Mrs. W.P.	34	Periods scanty followed by bleeding 27 days 1st time	+4	Late estrogenic, 14th day	5+ 14th day	2 weeks	600	3+ 14th day	12,000 2 months	6+ 16th day	Early estrogenic, 14th day

[1] Equine gonadotropin: 2000 I.U. per dose; three doses per month, administered on 9th, 10th, and 11th days of each cycle, for not longer than 4 months (12).

TABLE 3. CASES OF UTERINE FIBROIDS

Name	Age	Duration of Bleeding	B.M.R.	Endometrial Biopsy	Vaginal Smear Before Prolactin	Duration of Prolactin Treatment	Total Dosage of Prolactin	Vaginal Smear After Prolactin	Biopsy and Comments
							I.U.		
Mrs. G.H.	43	8 days, no bleeding previous 5 mo.	−5	Late estrogenic, 8th day	4+ 8th day	1 week	400	2+ 18th day	Early estrogenic, 18th day no surgery
Mrs. R.H.	24	18–19 days, 3½ years		Early estrogenic, 12th day	3+ 12th day	8 days	800	4+ 21st day	Late estrogenic 21st day no surgery
Mrs. W.L.	30	11 days, 3 months	+5	Cystic hyperplasia, 12th day	5+ 12th day	12 weeks	1100	3+ 18th day	Cystic hyperplasia, 12th day; hysterectomy
Mrs. D.W.	33	5 days, 20 day cycles, 3 months	+1	Late estrogenic, 10th day	5+ 10th day	4 days	300	3+ 26th day	No surgery
Mrs. R.M.	47	10–20 days, scanty 18 months	−7	Early estrogenic, 24th day	4+ 24th day	7 days	700	3+ 6th day	Early estrogenic, 24th day, no surgery
Mrs. A.F.	41	21 days, 1st time	+3	Late estrogenic, 22nd day	5+ 22nd day	3 weeks	600	3+ 21st day	No surgery
Mrs. L.Z.	46	8–12 days, usually early, 5 months	+4		4+ 26th day	12 weeks	700	3+ 26th day	No surgery
Mrs. H.Z.	43	10 days, 3 months	−5	Cystic hyperplasia, 12th day	4+ 12th day	5 days; 7 mo. later 7 days	300 700	3+ 19th day	Partial hysterectomy
Mrs. A.E.	48	Excessive, frequent, 2 years	+6	Early estrogenic, 19th day	3+ 19th day	14 weeks	1300	2+ 22nd day	Uterus not easily palpable; no operation
Mrs. R.M.	47	14 days, 6–8 week cycles			3+ 14th day	1 week	700	3+ 18th day	7 months after treatment menses normal; uterus smaller
Mrs. W.W.	49 49	2 weeks, 2 months		Late estrogenic, 10th day	4+ 10th day	5 days	500	2+	No surgery
Mrs. C.H.	44	10 days, 7 months	+3	Early estrogenic, 10th day	5+ 10th day	13 weeks	1100	3+ 17th day	No surgery
Miss E.P.	35	2 weeks, 11 years	−9	Late estrogenic, 18th day		3 weeks	800	4+ 18th day	No surgery
Mrs. M.B.	49	2 weeks, 2 months	−5	Cystic hyperplasia, 16th day	5+	4 weeks	800	3+ 18th day	No surgery
Mrs. R.S.	47	2 weeks, 2 months	+8	Late estrogenic, 21st day	5+ 21st day	3 weeks	1000	3+ 20th day	No surgery
Mrs. S.A.	33	3 weeks, monthly, 1 year	+6	Mild hyperplasia, 24th day	5+ 24th day	1 week	300	4+ 21st day	No surgery
Mrs. O.G.	58	1st in 18 months, 5 weeks	−7	Atrophic, 35th day	3+ 35th day	2 weeks	500	2+ 21st day	Atrophic, 21st day; myomectomy
Miss H.H.	37	15–20 days, 5 months	+1	Early estrogenic, 22nd day	3+ 22nd day	4 weeks	600	2+ 21st day	Atrophic, 21st day no surgery
Mrs. P.B.	32	10 days, 1 year	+14	Late estrogenic, 10th day	4+ 10th day	3 days	300	3+ 14th day	Intrauterine fibroid, size of walnut; partial hysterectomy

TABLE 3—*Continued*

Name	Age	Duration of Bleeding	B.M.R.	Endometrial Biopsy	Vaginal Smear Before Prolactin	Duration of Prolactin Treatment	Total Dosage of Prolactin	Vaginal Smear After Prolactin	Biopsy and Comments
Mrs. D.Z.	47	8–12 days, 21-day cycle, 5 months		Proliferative, 18th day	3+ 18th day	10 weeks	I.U. 700	3+ 24th day	1 year after therapy, fibroids seemed smaller; menses scanty; no flushes
Mrs. H.S.	43	Scanty, 10 10 days, 3 months	+3	Late estrogenic, 12th day	5+ 12th day	5 weeks	600	3+ 18th day	Diabetic; fibroid same size after 5 months; operation, intrauterine fibroid; follicle cyst
Mrs. R.S.	44	Heavy, 14 days, 2 months	−8	Cystic hyperplasia, 18th day	5+ 18th day	3 weeks	1300	3+ 18th day	Small fibroid; 3 months after beginning treatment uterus normal size; fibroid not palpable

was able to tolerate the lactogenic serum at a later time. The hormone is kept under refrigeration of 34 to 36° F.

RESULTS OF THERAPY

Twelve patients required only prolactin therapy to regulate excessive menstrual bleeding. Eleven of these were over 40 years of age.

Twenty-two patients received equine gonadotropin therapy after the excessive bleeding had been regulated by prolactin. Only two were over 40 years of age. Four patients became pregnant after the gonadotropin therapy was completed. This would seem to indicate that the antigonad effects of prolactin are temporary and harmless.

Twenty-two patients who had uterine fibromyomata received from 300 to 1300 I.U. of prolactin. All but 5 obtained relief with no further excessive bleeding. This seems important in conjunction with the control of functional bleeding, since it gives evidence that factors other than those now recognized may be responsible for excessive uterine bleeding. It was necessary to do partial hysterectomies for four of these patients and a myomectomy (intrauterine) for the fifth. There was at least one ovarian follicle cyst present in each of the five operative cases.

DISCUSSION

If an abnormally large amount of the lactogenic factor of the anterior pituitary exists, there is a disturbance of the control of the anterior pituitary over the normal routine of development of follicle and in corpus luteum, and consequently, of the usual cyclic changes in the endometrium. Estrogen inhibits the production of the lactogenic principle of the anterior pituitary, and conversely the lactogenic hormone inhibits estrogen production in the ovary. On this basis, it seems rational to suppose that if there is an actual or relative excess of estrogen in the blood, the administration of prolactin should have an antigonadotropic effect in preventing the continued formation of new estrogen by the ovaries. This seems to be borne out by the fact that normally lactating mothers do not ovulate, nor do they menstruate.

The antigonadotropic action of preparations of prolactin was shown in birds by Riddle and Bates (6), and Bates, Lahr, and Riddle (7). Dresel (8), and Lahr and Riddle (9) were able to suppress the estrous cycles in rats with preparations of prolactin. This has been confirmed by Evans, Simpson, and Lyons (10) with purified lactogenic hormone. In the latter experiments, the growth of graafian follicles was suppressed, but the healthy corpora lutea present in the ovary when injections were begun were maintained, and the luteal cells showed the hypertrophy typical of pregnancy or lactation. That the lactogenic hormone induced the luteal cells to form progestin was shown by Evans, Simpson, and Turpeinen (11). The latter workers, using hypophysectomized and adrenalectomized rats showed that the lactogenic hormone acted upon the persisting luteal tissue causing it to form progestin as proven by placenta formation. Thus, lactogenic hormone must be considered luteotropic in rats in the sense that it maintains and stimulates to function an already existing, healthy corpus luteum, although large doses of it have never been shown to cause the new formation of luteal tissue as does the proper combination of the other gonadotropic hormones (follicle stimulating and luteinizing factors). In explanation of its follicle-inhibiting action, Bates and Riddle have shown that prolactin inhibits the secretion (or effect) of the follicle-stimulating hormone of the pituitary.

It is possible that the lactogenic hormone may be

considered as acting in two different ways, since patients showing abnormal bleeding due to an insufficiency of progestin might be helped by its luteotropic action, whereas those who are under the influence of a hyper-functional follicular apparatus might conceivably benefit through its inhibiting action on the production of the follicle-stimulating hormone.

CONCLUSIONS

There is an important physiological relationship between the lactogenic factor of the anterior pituitary and the functions of the ovary and endometrium. The lactogenic hormone is antigonadal in its effects.

The use of the lactogenic hormone (prolactin), in a recent series of 34 cases of functional menorrhagia-metrorrhagia has controlled the bleeding successfully in every case.

Equine gonadotropin was used following prolactin for 22 of the 34 patients in order to improve their ovarian function.

Only 5 (23%) patients with uterine fibromyomata required surgery. The other 17 (77%), who had fibroid conditions improved satisfactorily with prolactin treatment only.

Evidence is presented that prolactin has a transitory, harmless effect physiologically, and that there may be other factors partially responsible for excessive uterine bleeding than those which are now recognized.

This method of controlling excessive uterine bleeding, was studied for a period of 4.5 years and is reported so that other clinicians may determine the advisability of further investigation of prolactin for the treatment of excessive uterine bleeding.

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The equine gonadotropins employed were Gonadin, supplied by Cutter Laboratories, Berkeley, Calif., and Anteron, supplied by Schering Corporation, Bloomfield, N. J.

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Functional Uterine Bleeding

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RICHARDSON (1) defines functional bleeding as that which appears in the absence of gross lesions at unexpected times or in abnormal amounts. The cause is unknown, but it is believed to be due to a dysfunction of one or more of the ovarian or pituitary hormones. It is an extremely bothersome syndrome both to the patient and to the physician. Its frequency and widespread occurrence are well known, and it is therefore of definite interest not only to the gynecologist and endocrinologist, but also to the general practitioner, internist and surgeon.

Its etiologic factors are obscure and the contributions of the experimental laboratory to its pathogenesis have been meager. No true pathological bleeding has been produced experimentally, although many menstrual and pseudomenstrual bleedings have been induced with hormonal agents both in woman and monkey (2).

Functional bleeding may occur from any type of endometrium, cystic and hyperplastic, proliferative, progestational or atrophic. Experimentally, neither the pituitary nor the ovary is essential for uterine bleeding, and Kurzrok (3) believes the responsible factors reside in the endometrium.

Up to recent times, the estrogen withdrawal theory or aberrant estrogenic function has been the basis of all etiological theories. However, it does not explain the bleeding that is clinically noted when continuous large doses of estrogen are given. Also the cystic glandular hyperplasia type, which constitutes probably one-third of all types of functional bleeding, is not satisfactorily explained by an excessive estrogenic supply. Kurzrok (3) points out that neither the blood nor the urine of such patients shows higher estrogenic titers. And furthermore, other tissues supplied by estrogens do not show the effects of overstimulation such as enlargement of the breasts or uterus. Kurzrok therefore feels that it is an endometrial affair, the endometrium taking more than its share of the estrogens and this in turn causing more estrogen to be produced by the ovary. And so the endometrium may be the cause of the cystic follicles so frequently found in the ovaries of such patients rather than the cystic follicles causing the hyperplastic endometrium.

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The many conflicting theories indicate the cause is unknown. We do know there must be some aberration of function in the ovaries or endometrium or both. No present theory can satisfactorily explain all types of functional bleeding. The factors involved are the endometrial vessels, the endometrium, the ovaries and the pituitary. The intrinsic relationship between these factors is not clearly understood. Indeed little is known of the physiology or hormonal effects of the endometrium itself.

My own view is that all women at some time or other may have some of these functional disturbances during their active sex-endocrine life. In many cases it is just a temporary phase and if some palliation and regulation can be carried out, nature will readjust her endocrine pattern and she will become 'regular' again. Hamblen (4) says 'normal women may have two to five anovulatory cycles a year. Minor menstrual irregularities are often normal for the individual and only when undesired sterility is related to these irregularities, or when there is a depleting hemorrhage, is therapy justified.'

ENDOCRINE THERAPY

The use of such endocrine substances as testosterone, chorionic gonadotropin, equine gonadotropin and a new combination—pituitary gonadotropic substance containing chorionic plus whole pituitary extract—have not yielded successful or desirable results.

Testosterone

Testosterone undoubtedly will check aberrant bleeding as demonstrated by Mazer and Mazer (5) and by Salmon and his associates (6). The *modus operandi* probably is by its counter depressing activity on the pituitary gland, and the consequent depressed ovarian activity. However, the expense of such therapy is of no little consequence. And more important are the frequent disturbing and embarrassing side effects, as the development of male characteristics such as hirsutism, atrophy of the breasts and change of voice. And, unhappily, not all of these side effects disappear with the discontinuation of treatment. Furthermore, we know it causes atrophic changes to appear in the ovaries and endometrium and the future endocrine balance may be permanently impaired.

Pituitary Gonadotropic Substances

The pituitary gonadotropic substances theoretically should be a satisfactory type of treatment, because they are supposed to exert trophic influences upon an ovary which for some reason or other is not functioning properly. However, they are the most disappointing form of all endocrine therapy in this field.

Chorionic Gonadotropin

Chorionic gonadotropin (which is also known as APL pregnancy urine extract, luteinizing substance) has been found sadly lacking in effect in checking and curing functional bleeding. Indeed it has been found wanting in most fields of gynecic endocrinology. And it has even been known to cause ovarian damage through the formation of atretic follicles. Geist (7) and others have found it to be useless in the treatment of abnormal uterine bleeding, and any beneficial effects as reported by some are said to be merely coincidental. Kurzrok (3) uses small blood transfusions in checking functional uterine bleeding. The donor is a pregnant woman in her middle trimester. He feels the value resulting is by reason of the high concentration of pregnancy gonadotropin at this period. But it may very well be due to the high level of estrogens at this time or to some other unknown factor.

Equine Gonadotropin

Equine gonadotropin (developed from pregnant mare's serum) has experienced a more popular reign, but it is of little or no more value. It is supposedly a potent gonadotropic substance, as evidenced by causing ovulation in experimental animals. Ever since Davis and Koff (8) in 1938 claimed they could produce artificial ovulation in women by means of this hormone, there has been a tremendous volume of this material used throughout the country. Sevringhaus (9) also claimed somewhat similar findings. Hence it was used in many instances of ovarian failure such as sterility, menorrhagias and metrorrhagias, amenorrheas, and even dysmenorrhea.

However, evidence is now accumulating to show that it is very doubtful whether one can ever produce an artificial ovulation or improve ovarian function by this substance. Geist (10) and his associates in a careful analysis of 91 cases followed by observation at laparotomy state they have never seen an ovulation result from its use. Novak and Hofbauer in discussing the above work of Geist's say it is of no proven value and should be discarded. Karnaky gave huge doses to normal women and never observed a change in endometrial pattern. Sexton and Vogt (11) reported only meager results in the treatment of menorrhagia with its use. Erving (12) and his associates found 81 per cent of their cases were unaffected by the use of equine gonadotropin and in no case was there evidence of stimulation of ovulation. And recently Gray (13) in evaluating equine gonadotropin found it of value in only 50 per cent of his cases of metrorrhagia, a figure easily duplicated by spontaneous cures.

Combined Gonadotropins

The other gonadotropic substance which is becoming popular at present is the chorionic gonadotropin in combination with a whole pituitary extract synergist.[1] Its commercial name is Synapoidin. In a preliminary report, Mazer and Ravetz (14) claim they arrested dysfunctional bleeding in 14 of 18 patients and evoked menstrual flows in 19 of 23 severely amenorrheic women, some of whom had not menstruated for years, despite all other forms of treatment. Karnaky states he has produced definite changes in endometrial patterns and menstrual changes in normal women. Geist (10) has not found it of much more value than any of the other pituitary hormones.

I have had no experience with its use in the menorrhagias and metrorrhagias, but have used it in a few cases of amenorrhea and sterility. Bleeding has recurred in two amenorrheic women of four so treated. It is too early to determine its value in my sterility cases, although it has not to date changed the anovulatory endometrial pattern of one to that of a normal secretory state. However, I do believe of all the pituitary gonadotropins it is the most promising. But it should be remembered that other substances experienced a similar flurry of popularity. And as Mazer and Ravetz (14) have pointed out, it should be used with care, for serious side effects such as increased size of ovaries and cystic ovaries may result from its indiscriminate use in young girls.

Thyroid

A discussion of functional uterine bleeding must include a word on the use of thyroid. I think this is by far and large one of the most valuable and most forgotten endocrine substances. There is a tendency to use the newer, fancier and more expensive endocrine products in place of this simple and tested substance. It is of value chiefly in the menorrhagias of the younger age groups. In fact, some believe it is almost specific in these cases. Of course, its value in a true hypothyroid case is unquestioned. But I think it is of inestimable value in the borderline type of case as well. I use it in menorrhagias of the teens and early twenties and in all other cases in which improvement is not rapid or marked in conjunction with other endocrine products. Karnaky uses it to tolerance as a routine measure in conjunction with large doses of diethylstilbestrol.

[1] The combined chorionic and pituitary gonadotropin preparation (Synapoidin) is manufactured by Parke, Davis & Co, Detroit, Mich.

Corpus Luteum Hormone

At one time corpus luteum hormone (progestin, progesterone), was thought to be the answer for the cure of menorrhagias, because it is supposed to have a quieting effect on the uterus, and it is supposed to be an antagonist to estrin. This thought arose chiefly because most dysfunctional bleedings were of the cystic hyperplastic type, and all were anovulatory, indicating the absence of corpus luteum activity. However, the results were just the opposite as shown by Hamblen (15), Gillman (16) and Zondek and Rozin (17). They showed that progesterone will aggravate a menorrhagia and even cause bleeding in a normal woman in the intracyclic period. However, Weisbader (18) has recently reported that pregneninoline (a synthetic progesterone) has proved effective in checking functional uterine bleeding. He gives large doses, 250 to 350 mg. in divided doses of 50 mg. daily to check the bleeding, and then uses 200 to 240 mg. in divided doses during the second half of the succeeding periods to prevent the recurrence. It is difficult to see the mechanism involved here unless it be by (*a*) an inhibitory action on the pituitary, (*b*) an endocrine imbalance causing a relative increase or decrease in the estrogenic level or (*c*) making the endometrium less refractive to the estrogenic level. On the other hand, Gaines (19) and his associates found pregneninoline of no value in functional uterine bleeding and concluded it had no suppressing effect on the menstrual cycle.

The Estrogens

Theoretically, it would seem that estrogenic substances would aggravate an existing bleeding state because of its proliferative action on the endometrium. However, it is a clinically known fact that estrogens in large doses will check uterine bleeding, either normal or abnormal.

It is obvious that the estrogens play an important rôle in the bleeding mechanism, for even though both ovaries and the pituitary are absent, bleeding can be induced experimentally with estrogens. Furthermore, the absence of estrogens as the result of castration, leads to an atrophic endometrium; the endometrium is atrophic also in the pre-pubescent girl. In pregnancy, during which there is a high estrogenic level, there is a period of physiologic amenorrhea. Apparently there is a level at which gynecic function proceeds normally and cyclically. Karnaky (20) demonstrated an estrogenic hormone bleeding level, above or below which amenorrhea results. This level may vary in different women because of interrelationship with other hormones or because of nervous factors. Karnaky, by giving large doses of estrogenic material, could check abnormal or normal bleeding at will. Upon withdrawal of estrogenic hormone, the blood level drops until the bleeding level is reached, and uterine bleeding ensues. The bleeding which is clinically noted when continuous doses of estrogenic hormone are given, or in cases in which the ovaries are cystic, is explained by the fact that the hormone fluctuates at the bleeding level, the estrogen being constantly metabolized by liver, kidney and uterus. However, if at any time large doses of estrogen would be given, the bleeding would promptly cease (20).

Up to this point Karnaky has ably explained a most likely theory of bleeding. But the simple elevation of the blood estrogen above the bleeding level cannot explain the permanency of regular menstruation occurring in those women in whom large doses of estrogen have checked the functional bleeding. A temporary benefit in checking the bleeding is obvious, yet Karanky has reported that 87 per cent of his patients, in whom uterine bleeding has been checked with large doses of estrogen, have afterwards had normal menstrual periods. My observations have been the same. The explanation for this phenomenon is apparently the effect of large doses of estrogen on the pituitary, which Karaky failed to discuss. Estrogenic substances are of value in the menopausal patient by virtue of the fact they inhibit the hyperpituitarism which apparently is the cause of the vasomotor imbalance. Large doses of estrogens seem to have a marked contra-physiologic effect on the pituitary gland. This, in turn, will cause a cessation of gonadotropic stimulus to the ovary, and the ovary will, for a period, be inactive. This conclusion is supported by the fact that Karnaky frequently has observed that initially cystic ovaries are no longer so in bleeding patients after large doses of estrogens are given. I have observed smooth ovaries at laparotomy in patients who have received large doses of diethylstilbestrol prior to laparotomy. It is possible that the period of non-activity in the ovary is associated with the regular menstrual periods which follow, since some aberrant ovarian factor may be removed. This idea is substantiated by Friedman's (21) theory that small doses of irradiation to the ovaries of women who have irregular bleeding or amenorrhea are benefited, not because roentgen rays are stimulating, but rather because they may destroy some inhibiting factor in the ovary. He further supports this theory with the fact that Stein and Cohen (22) have treated amenorrhea and sterility by removing surgically the cystic portion of both ovaries. Hence all three of these procedures, *a*) contraphysiologic estrogen *b*) irradiation and *c*) excision of cystic portions of the ovary may remove inhibiting factors in the cystic portion of the ovaries and cause a normal ovarian function to ensue.

Therefore, large doses of estrogens are effective in

checking and curing functional bleeding, by *a*), raising the estrogenic hormonal blood level above the bleeding level and hence causing an immediate cessation of bleeding; and *b*) inhibiting the gonadotropic influences of the pituitary and giving the ovary a period of rest, thereby tending to restore permanently normal ovarian function and menstruation.

Clinically, Hamblen (23) and his associates use large doses of estradiol benzoate or some natural estrogen to check uterine bleeding, and follow this with a cyclic treatment consisting of the administration of estrogens in the first half of the cycle and corpus luteum hormone, as progesterone or the synthetic anhydrohydroxy-progesterone, in the second half. By this means they hope, after having checked the bleeding, to maintain an artificial pituitary-ovarian rhythm which will tide the patient over until the normal ovarian-pituitary balance occurs. Large doses of progesterone or anhydrohydroxy-progesterone are used, an average of 400 mg. of anhydrohydroxy-progesterone per period.

Karnaky (20) checks uterine hemorrhage with large doses of diethylstilbestrol. If bleeding is severe, he injects from 10 to 25 mg. of diethylstilbestrol in oil into the anterior cervix. If bleeding is not severe, he gives the patient 25 5-mg. tablets and instructs them to take one a night for 20 nights. This usually checks the bleeding promptly. The patient then has 5 tablets which are used to control the inevitable withdrawal bleeding which occurs 2 to 8 days after the 20 days of therapy. About 14 to 21 days later, she will experience a normal period and in 87 per cent of his cases the rhythm will again become normal. He also uses thyroid to the point of tolerance, 0.25 to 30 grains daily.

In my experience, a combination of these two methods has proven most successful. Large doses of diethylstilbestrol are used to check the immediate bleeding. This is followed with Hamblen's cyclic treatment, using, however, diethylstilbestrol instead of a natural estrogen, and anhydrohydroxy-progesterone instead of the natural progestin, to prevent a recurrence of bleeding. Possibly the use of the cyclic therapy to prevent recurrence is unnecessary, as Karnaky suggests, and possibly the progesterone alone is necessary, as Hamblen later used.

I generally prescribe 5 to 10 mg. daily of diethylstilbestrol, depending on the severity of the bleeding, for 15 consecutive days. The patients are advised to take the medication with a glass of milk at night before retiring. This will usually stop the bleeding promptly within 5 to 10 days. Some 5 to 9 days after discontinuing treatment the withdrawal bleeding occurs. This is not to be confused with a regular menstrual period and usually needs no treatment to stop it. Following this, the patient will usually experience a normal menstrual period some 2 or 3 weeks later. The patient is then instructed to take 2 or 3 mg. of diethylstilbestrol in divided doses from the 10th to the 13th day of the cycle. Beginning on the 14th day the patient takes 10 mg. of anhydrohydroxy-progesterone daily for 10 days. If bleeding ensues before this 10-day period has elapsed, she is instructed to stop the drug. This 100 mg. of anhydrohydroxy-progesterone is less than the accepted amount necessary to produce a progestational endometrium. Thyroid is used when indicated, as previously outlined.

I have recently treated 25 patients by such a regime. In 21 the bleeding was satisfactorily controlled and the patients resumed normal cyclic menstruation. Of these 21, four have since become pregnant within a period of 4 months of the dysfunctional bleeding. Of the 4 patients who failed to respond to treatment bleeding was checked in 2 by curettage; hysterectomies were performed on the other 2. Both of the patients on whom hysterectomies were performed were 40 years of age.

The treatment as outlined above is effective in checking bleeding and regulating menstrual periods. I do not believe it is harmful to the delicate endocrine mechanism of the human female. Gillman (24) has observed massive follicular atresia in baboons given large doses of estradiol benzoate. I have not observed this phenomenon at laparotomy in women following estrogen therapy. The fact that these women experience regular periods after their treatment indicates that no harm is done. Furthermore, it is commonly observed that those women, who are given diethylstilbestrol to inhibit ovulation and so prevent dysmenorrhea in the succeeding period, experience a return of dysmenorrhea as soon as ovulation is not inhibited for that particular month. This would indicate the ovary is not functionally damaged or greatly changed. A complete functional recovery is possible in a certain percentage of cases as is evidenced by the recurrence of a secretory type of endometrium and by subsequent pregnancy. In addition to these advantages, this mode of therapy is inexpensive and oral.

These large doses of diethylstilbestrol may occasionally cause nausea. This can be reduced to a minimum by giving the medication at night with milk. As treatment is continued the nausea frequently disappears. Also, occasionally, it may cause vaginal soreness and backache, but neither of these side effects is as distressing as the prolonged bleeding for which the patient seeks relief.

It should always be remembered that a large proportion of these menstrual irregularities are but passing episodes in the sex-endocrine life of a woman. If such patients are aided through these periods, a large percentage will again resume a normal ovarian-

pituitary balance with the consequent menstrual regularity and, perhaps, fertility. Conversely, I believe, if nature, after a few months of artificial therapy, does not take over, then it is not in the power of present-day endocrine therapy to effect a recovery.

RADIUM AND RADIATION

I would hesitate to use either radium or roentgen-rays in the treatment of functional uterine bleeding for several reasons. First, even in the smallest doses they have a depressing effect on ovarian activity, and in so treating an already under-functioning ovary, little hope can be held for a satisfactory functional recovery. Secondly, many cases of bothersome bleeding occur in the third and fourth decades, and the results of radiation are notoriously poor in this younger age group. Randall and Lovelady (25) of the Mayo Clinic reported failure in 40 to 50 per cent of the cases in those age groups. Of course, in that group over 40 years of age, treatment with radium or roentgen-rays has a definite place. Thirdly, the dividing line between sub-sterilizing doses and those causing permanent amenorrhea and sterility is so uncertain that not even competent radiologists will guarantee the results. And, lastly, in those women who regain function and later become pregnant, the percentage of abortion is questionably high.

I have had no experience with low-dosage irradiation to the pituitary and ovaries. There have been some glowing reports (26, 27) as to its success. But the fact remains that its usage has not been widespread and we know little of its after effects.

CURETTAGE AND HYSTERECTOMY

Curettage should be mentioned. I feel that curettage has a definite place in the treatment of functional uterine bleeding. Briefly, there are a few definite indications for it: *a*), In those women above the age of 37 in whom a diagnosis of malignancy, polyps or submucous fibroid is always a definite possibility; *b*), in those women who are bleeding very profusely and for their general condition it is necessary to stop this promptly; *c*), in those women in whom conservative therapy has failed. I do not believe one curettement, with a dull curette and no strong astringents afterwards, can harm an endometrium and it may yield valuable information. In many instances this may effect a permanent cure. However, repeated curettements or the use of sharp curettes, can produce a scarring and fibrosis of the endometrium; this is to be deplored.

Hysterectomy will be needed in only a very few cases. In my opinion it is preferred to radiation before the age of 40 as it preserves ovarian function for at least a few years.

SUMMARY

An effort has been made to review briefly the present day status of the causes and treatment of functional uterine bleeding. It has been shown that the etiologic factors are obscure. Such endocrine substances as testosterone, progesterone and the numerous gonadotropins have been unsatisfactory or undesirable as therapeutic measures for the several reasons stated. The author believes that thyroid is of considerable therapeutic value, although it has been recently underestimated. On the basis of the estrogenic theory of uterine bleeding, diethylstilbestrol has been used in large doses to check immediate bleeding, followed by cyclic diethylstilbestrol and anhydrohydroxy-progesterone therapy to prevent a recurrence. The result of this type of therapy in 25 cases is presented. Radiation, frequent curettage and hysterectomy should play a minor role in the therapy of functional uterine bleeding.

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Comparative Clinical Effects of Orally Administered Alpha-Estradiol and Diethylstilbestrol on Postpartum Engorgement of the Breast

[Comparative Action of Estrogens]

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Oral doses of other estrogens comparable to those of diethylstilbestrol have not been employed extensively because of the expense involved or the difficulty in obtaining a non-toxic solvent that would insure efficient absorption. Since previous experience with diethylstilbestrol has established a measuring stick for evaluating estrogenic activity, a series of 156 puerperal women have been given diethylstilbestrol or α-estradiol and the effects on breast engorgement compared.

PROCEDURE

The relative effectiveness of orally administered α-estradiol and diethylstilbestrol on breast engorgement was ascertained, respectively, in 61 and 95 women; 79 of the latter number were included in a previous report (1). In addition the results were compared with conditions in 75 women who received no medication. Approximately 60 per cent of each group were primipara. The age range was from 14 to 48 years with the majority under 30 and only two were 40 years or older. Therapy was begun within the first 36 hours post partum and in all but 10 within 24 hours. In the majority of instances α-estradiol was administered at regular intervals day and night for 4 days, while diethylstilbestrol was usually given once daily for 1 to 6 days. The former was dissolved in propylene glycol and placed under the tongue. The patient was requested to lie with the head turned to one side and cautioned not to swallow for five minutes. Originally the propylene glycol contained 0.5 mg. of α-estradiol per cc., but it was soon learned that larger doses were required. This necessitated giving so much of the solution that it ran down the throat where it was probably not absorbed or was destroyed or inactivated in the stomach. Subsequently this difficulty was largely eliminated by employing a solution containing 5 mg. per cc. Diethylstilbestrol was given either in enteric-coated or uncoated tablets.

Medication was given to patients who preferred not to nurse their children or who had stillbirths, without further selection.

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RESULTS

In a previous study (1) it was noted that breast engorgement could usually be inhibited if diethylstilbestrol was given within the first 24 hours postpartum and continued for 4 or 5 days. Tables 1 and 2

Table 1. Results of orally administered alpha-estradiol on breast engorgement

Number of Cases	Dosage in Milligrams		Results			
	Daily	Total	Good	Fair	Failure	
					Number	Per cent
13	0.75 to 0.17 t.i.d.	8.5 to 2.1	1	2	10	77
10	0.75 to 0.17 q. 6 hr.	7.5 to 1.8	1	7	2	20
13	1.7 q. 4 hr.	45 to 30	7	5	1	7.7
12	1.7 q. 6 hr.	30	3	8	1	8.5
13	2.5 q. 6 hr.	40	11	2	0	0.0
Totals 61			23	24	14	22.9.

TABLE 2. RESULTS OF ORALLY ADMINISTERED DIETHYLSTILBESTROL ON BREAST ENGORGEMENT

Number of Cases	Dosage in Milligrams		Results			
	Daily	Total	Good	Fair	Failure	
					Number	Per cent
41	5 q.d.	5	24	13	4	9.8
15	10 q.d.	20 to 10	6	3	6	40.0
22	10 to 5 q.d. or b.i.d.	35 to 25	15	6	1	4.5
17	10 q.d.	50 to 40	15	2	0	0.0
Totals 95			60	24	11	16.6

indicate that α-estradiol produced effects comparable to those of diethylstilbestrol when the larger doses were employed, but there was a higher percentage of failures with small doses of α-estradiol. Previous experience revealed that frequent daily doses of diethylstilbestrol did not increase appreciably the effectiveness of the drug. On the other hand, α-estradiol in divided doses at short intervals was more effective than a single daily dose of the same magnitude. The less favorable results obtained with 20 to 10 mg. of diethylstilbestrol followed the use of non-coated tablets. This suggests partial destruction or inactivation of the drug in the stomach.

Among the mothers receiving at least 40 mg. of either drug, none had breast engorgement. By contrast, mastalgia appeared in 97 per cent (73 of 75 cases) of those not treated.

A 'fair' result indicates discomfort for 12 hours or less, while a 'failure' denotes that symptoms persisted 24 to 72 hours. Among the untreated group, the period of painful engorgement averaged 36 hours.

Lactation was usually diminished or delayed, but was never prevented entirely by either drug.

Salmon et al. (2) did not describe toxic effects, including nausea and vomiting, from the use of α-estradiol. The authors also observed no undesirable reactions.

SUMMARY AND CONCLUSIONS

Sixty-one postpartum women were given α-estradiol in propylene glycol sublingually to test the effect on breast engorgement as compared with that produced by diethylstilbestrol. Comparable total dosages of both drugs given over the same period effected similar results provided the α-estradiol was administered in divided doses at regular intervals throughout the day and night as contrasted to the same quantity of diethylstilbestrol employed once daily. Initiation of lactation was usually delayed, but not inhibited entirely. Toxic effects were not observed.

The use of α-estradiol has certain disadvantages, as compared with diethylstilbestrol, such as the need to give medication frequently, and the greater expense of the drug.

The diethylstilbestrol was supplied through the courtesy of Dr. J. A. Morrell of E. R. Squibb and Son, New Brunswick, N. J. The α-estradiol was supplied by Dr. Edward Henderson of the Schering Corporation, Bloomfield, N. J.

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Effect of Estrogenic Therapy on Decubitus Ulcers of a Large Rectocele

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MANY AUTHORS have demonstrated the effect of estrogens upon the vaginal epithelium. Papanicolaou and Shorr (1) have noted a proliferation of the vaginal epithelium of menopausal patients receiving estrogenic therapy, by examining vaginal smears. Geist and Salmon (2) have correlated the alterations in the vaginal smears with histological studies of the vaginal mucosa. On the basis of these changes, Schockert (3) and many others advocated intramuscular injections of estrogenic substances for the treatment of atrophy of the vulva and vagina. Claften (4) found the estrogens to be effective when administered locally. Later, Mishell and Motyloff (5), and Finkler and Antopol (6) obtained favorable results with the local application of estrogenic ointment in cases of senile vulvo-vaginitis.

The following case illustrates the effect of estrogens upon decubitus ulcers of a huge rectocele in a young woman with prolonged amenorrhea.

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CASE REPORT

Mrs. L.O., 27 years of age, was referred for gynecological opinion on Oct. 11, 1940, with a protrusion at the vulva and a history of vaginal staining of 6 months duration. The primary condition for which she was hospitalized was rheumatic cardiac disease with decompensation. She had had two difficult operative deliveries 6 and 4 years ago. Her last menstrual period occurred 2 years ago.

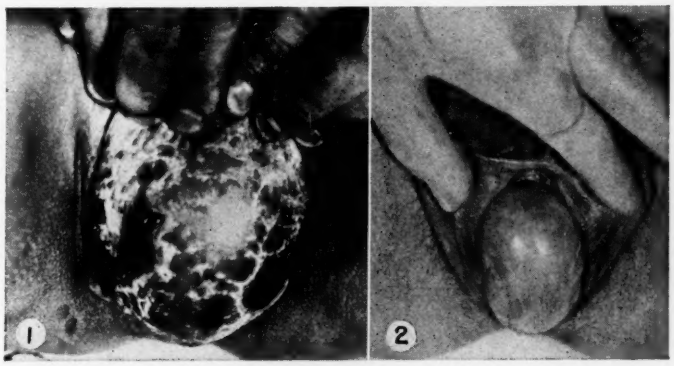

Fig. 1. HUGE RECTOCELE WITH ULCERATIONS AND ATROPHY OF THE MUCOSA BEFORE ESTROGENIC THERAPY.

Fig. 2. APPEARANCE OF THE VAGINAL MUCOSA, SHOWING COMPLETE HEALING OF ULCERATIONS, 7 WEEKS AFTER ESTROGENIC THERAPY WAS BEGUN.

Pelvic examination revealed a huge rectocele about 10 cm. in diameter protruding through the introitus. On the surface were two irregular ulcerations, each about 3 cm. in length, and 1 cm. in width. The mucosa of the rectocele was inflamed, atrophic, and fissured (fig. 1). The cervix was found behind the symphysis. The uterus was normal in size and retroverted. The adnexae were not palpated.

For two months the patient was treated with bed rest, topical applications of silver nitrate to the vaginal ulcerations and vaginal packing with vaseline gauze to support the rectocele. There was no appreciable improvement during this time.

Estrogenic therapy was begun Dec. 12, 1940. An injec-

tion of 2,000 R.U. of estradiol benzoate[1] was given three times a week for a month. In addition, 2,000 I.U. of estrogen in ointment form[1] was applied locally every other day for three treatments. During the second week a daily application of 2,000 I.U. was similarly given. A daily dosage of 5,000 I.U. of estrogen was applied to the vaginal ulcerations and mucosa during the third and fourth weeks. After each local treatment the rectocele was replaced in the vagina and held there with vaseline gauze.

Within a week the ulcerations were healing by epithelialization and the mucosa appeared thicker and less fissured. On Jan. 17, 1941, five weeks after estrogenic therapy was begun, the ulcerations were found to be completely healed. The vaginal mucosa appeared normal and there was a marked decrease in the size of the rectocele. A photograph taken Feb. 3, 1941, illustrates the improvement (fig. 2). Simultaneously, the patient was treated medically for cardiac decompensation, and a decrease in the ascites and edema resulted. When last seen, Nov. 28, 1941, the vaginal mucosa of this patient was entirely intact and normal in appearance.

[1] The estrogenic preparations (Dimenformon benzoate ampoules and Menformon dosules) were supplied by Roche-Organon, Inc., Nutley, N. J.

CONCLUSIONS

This case illustrates the healing effect of estrogenic substances on ulcerations and atrophy of the vaginal mucosa of a huge rectocele in a young cardiac patient with amenorrhea of 2 years duration.

We feel that rest in bed, replacement of the rectocele and improvement in the cardiac status, with diminution of the ascites and edema, undoubtedly played an important rôle in the healing of the vaginal ulcers. Nevertheless, estrogenic therapy, with its proliferative effect on the vaginal mucosa, unquestionably hastened healing. Estrogenic therapy may be utilized for hastening the healing of mucosal ulcers of cystoceles, rectoceles and uterine prolapse in preparation for operation.

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Studies on the Etiology of Human Breast Disease

I. Urinary Excretion of Follicle-Stimulating Hormone, Estrogens and 17-Ketosteroids in Adolescent Mastitis of Males[1]

[Adolescent Mastitis]

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ADOLESCENT or puberty mastitis in the male is akin to that normally seen at the onset of breast development in young girls. In the male it usually appears between the 12th and 16th year. It is characterized by the presence of a well defined, freely movable discoid or round palpable mass of breast tissue, closely associated with the areola. The mass may vary in size from less than 1 centimeter to 5, but as a rule is 2 to 3 centimeters. The overlying areola and nipple may be enlarged. Tenderness is not uncommon and may be the first and only sign noted by the patient. The process is usually unilateral at the onset, but may affect both breasts simultaneously or successively. Adolescent mastitis must be distinguished from gynecomastia in which the size, contour and elements approach that of the normal adult female breast; and from enlargement of the breast due entirely to adipose tissue such as is seen frequently in adiposo-genital dystrophy and in eunuchs.

Adolescent mastitis in the male occurs more commonly than is generally recognized. Jung and Shafton (1) in approximately 1000 examinations found that the appearance of a palpable mass of mammary tissue is an integral part of the process of puberty. It is not seen more often because of the frequently transient character of the process, which may arise and regress within even a month. The cases which are usually seen by physicians are those in whom growth is rapid, tenderness is marked, or the duration is prolonged. These lesions occur at a time when sexual metamorphosis is relatively rapid as a result of hormonal stimulation (2). It seemed possible therefore that a temporary imbalance of various endocrine factors might be responsible and that this might be reflected in the excretion rates of the sex hormones and their end products. Consequently a study of the urinary excretion rates of the follicle-stimulating hormone of the anterior hypophysis (FSH) as well as of estrogens and 17-ketosteroids was carried out. There were 21 subjects, ranging in age from 12 to 16 years, who entered the clinic for examination because of disturbances of the breast. In many instances it was not possible to obtain more than one 24-hour specimen for assay. Although frequent titrations are not as necessary in boys as in girls (2) it would have been desirable to have more determinations, especially since spontaneous regression was common in this series. The findings in these cases were compared with a large series of assays, which were made on normal boys and girls in the same age range (2).

Technique of Extraction and Assay of the Hormones

Follicle-stimulating hormone, prolan A, gonadotropic hormone (FSH). FSH was precipitated from the urine by means of ethyl alcohol, using the original method of Ascheim and Zondek. Assay was carried out on inbred immature pure strain female mice (Bar Harbor C 57) between 19 and 21 days old and weighing between 6 and 8 grams. Vaginal opening was used as the criterion of gonadotropic activity in the extract. This type of end point is perhaps not as sensitive as that of follicle stimulation or that of increased ovarian or uterine weight. It was chosen purposely, however, so that a positive response would indicate a significant elevation. In the earlier work the urine was so concentrated as to detect a minimum of 80 mouse units (M.U.) per 24 hours. This level proved

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[1] This is paper No. 555 of the Cancer Commission of Harvard University.

TABLE 1. SEX HORMONE EXCRETION LEVELS IN ADOLESCENT MASTITIS.

Patients					Values in Normal Individuals							
					Males				Females			
Name	Age	Estrogens	17-Ketosteroids	FSH	Estrogen, I.U. Average	Estrogen, I.U. Range	17-Ketosteroids, mg. Average	17-Ketosteroids, mg. Range	Estrogens, I.U. Average	Estrogens, I.U. Range	17-Ketosteroids, mg. Average	17-Ketosteroids, mg. Range
	years	I.U.	*mg.*	M.U.								
E.F.	12	54	6.0	N.D.	30	10–60	13.0	9–15	240	30–400	10.2	6–13.2
P.M.	12	144	8.5	N.D.								
		172	9.0	>25								
		202	10.0	N.D.								
A.S.	12	48	7.6	<80								
T.M.	12	40	6.0	<35								
		50	6.5	<60								
F.P.	12	10	13.8	N.D.								
		21	14.4	N.D.								
A.S.	12	100	9.9	>40								
S.D.	13	96	15.6	<80								
		72	16.0	<80								
		178	13.2	<30					300	40–500	10.6	6–13.2
		248	25.2[1]	<30								
T.C.	14	204	6.5	<20	40	20–80	15.0	10–19	380	50–600	11.4	6–15.0
		124	8.8	<25								
M.B.	14	200	12.0	<25								
		50	11.8	N.D.								
		190	16.0	<25								
N.P.	14	48	7.2	<80								
H.C.	14	18	10.0	<20								
		105	8.4	>30								
R.B.	14	48	6.6	<40								
H.S.	14	15	9.5	<40								
G.G.	14	92	19.5	>95								
M.A.	15	74	14.4	<50								
		20	13.5	<80								
W.H.	15	30	9.0	<20								
T.M.	15	90	9.0	N.D.								
		60	6.9	N.D.								
L.C.	15	105	14.3	26								
P.H.	16	20	16.0	<80								
I.A.	16	30	14.4	<20								
		430	13.0	<25								
		192	19.8[1]	>60								
H.H.	16	160	13.5	N.D.								

[1] On treatment with testosterone propionate.
N.D., not determined.

to be too high to detect its presence in most cases. Later on, therefore, the minimal level tested was between 20 and 40 M.U. One mouse unit is defined as the minimal amount of material which, when injected in five equal parts over a period of 48 hours, will produce vaginal opening in the animals 96 hours after the first injection.

Estrogens and 17-ketosteroids. The urinary estrogens

and 17-ketosteroids were extracted by the method of Smith and Smith (3). This consists of preliminary hydrolysis with hydrochloric acid and subsequent extraction with benzol in a continuous extractor. The estrogens were separated from the 17-ketosteroids, using in principle the method of Gallagher et al. (4). With this technic the 17-ketosteroids, which are insoluble in alkali, remain in the neutral fraction and are thus separated from the phenolic estrogens which are soluble in alkali (NaOH). The crude total estrogens and 17-ketosteroids were assayed without further purification.

The estrogens were assayed on inbred pure strain ovariectomized mice (Bar Harbor C 57) or rats (Slonaker) with a minor modification of the Allen-Doisy method: estrogens are expressed as international units equivalent in biological activity to crystalline estrone.[2]

The 17-ketosteroids were measured colorimetrically. We have used this method to estimate the androgenic activity in the urine. The 17-ketosteroids include the androgens, such as androsterone, and dehydroisoandrosterone and also closely related compounds which are not androgenic in biological activity when they are excreted, but many represent catabolic changes of such compounds. The development of the color for titration was essentially that described by Oesting (5), except that certain conditions such as temperature, light and purity of reagent were kept as uniform as possible. The reaction which was originally described by Zimmerman (6) is based on the ability of meta-dinitrobenzene to produce a color reaction quantitatively with substances containing the $-CH_2CO$ grouping in alkaline alcoholic solution. Readings were made on the Evelyn photoelectric colorimeter and the values are expressed in terms of milligrams equivalent to that of crystalline androsterone.[3]

RESULTS

The levels of hormonal excretion are given in table 1. They represent three different groups: *a*), The values obtained in the groups under consideration. *b*), Average values and range of values for boys of the same chronological age. *c*). Average values and range of values for girls of the same chronological age.

DISCUSSION

The results indicate that in most of the cases there was an abnormality in the urinary excretion rate of either the estrogens, the 17-ketosteroids or both when compared with the normal controls. The 17-ketosteroid excretion was frequently below, or at the lower limits of the average range, whereas the estrogen excretion was significantly elevated in almost one-half of the patients. When each case is considered individually it can be seen that some have both a lowered 17-ketosteroid and an elevated estrogen excretion, while others display only an abnormal estrogen or depressed 17-ketosteroid output. A few of the patients had normal rates for both types of hormones. It seems, therefore, that there is no consistent pattern of excretion if only a single type of hormone is considered. However, consideration of the ratio of the 17-ketosteroids to the estrogens seems to clarify the situation. In the patients who have atypical excretion rates of one or both of the hormonal groups there is a definite shift of the ratio toward the feminine type i.e. estrogen levels out of normal proportion to the 17-ketosteroid levels. This is most obvious in those individuals in whom the estrogens were elevated in the presence of lowered 17-ketosteroids. The significance of the shift in ratio is shown clearly in the tables by comparison of the levels of the patients studied with normal boys and girls of the same chronological age. It is interesting to note that in many instances the excretion rates of the boys with mastitis fall into the same range as those of girls of the same age. Since girls mature somewhat earlier than boys such a comparison may not be strictly analogous, but the trend is demonstrated.

It is true that in some of the cases, the levels for both the 17-ketosteroids and estrogens were within the average range. This is difficult to explain in the light of the other findings. Nevertheless, there are several possibilities. *a*), The process may be sufficiently advanced or of such long duration, that in spite of normal levels at the time of assay, the lesion is irreversible and therefore falls into the groups which are seen for the first time in later life. *b*), The assays may have been made after the exciting factors. have returned to normal, i.e., regression of the lesion was taking place when the determinations were made. As far as can be ascertained on such a small group, there is no direct correlation between the duration of symptoms, speed of regression and the values obtained.

Assays for FSH were made in an effort to detect hyperactivity of the anterior pituitary gland. In several cases an elevated level was found, but even though this may be suggestive of hyperactivity, the data were too few to be of significance. This is espe-

[2] Crystalline estrone was supplied for standardization through the courtesy of Dr. E. A. Sharpe, Parke Davis & Co., Detroit, Mich.

[3] The values which represent the crude total levels for 17-ketosteroids cannot be compared to those of other writers. This is due to the fact that the methods of titration and extraction in different laboratories vary and thus control levels for each individual group may deviate considerably from one another.

Crystalline androsterone for calibration of standard curves was supplied through the courtesy of Dr. Ernst Oppenheimer of Ciba Pharmaceutical Products, Inc., Summit, New Jersey and Dr. Erwin Schwenk of the Schering Corporation, Bloomfield, N. J.

cially true since males of this age group may show elevated values without puberty mastitis (2). An increase in FSH may be an index of the activity of other pituitary hormones such as the poorly understood mammogenic hormone, which is a possible etiological factor.

From the data presented it appears that adolescent mastitis in males occurs in the presence of a hormonal imbalance in which the influence of the estrogens plays an important rôle. Analogous lesions can be produced in male rodents and likewise in the human male with estrogenic hormone (7). Several observers have reported similar changes after the administration of testosterone (8, 9). The possibilities involved are beyond the scope of this paper. Similar studies on gynecomastia in young men and on chronic mastitis in older males will be published in the near future in an effort to further clarify these changes.

CONCLUSIONS

Adolescent mastitis in males appears to be associated in many instances with atypical urinary excretion rates of the estrogens and 17-ketosteroids, probably as a result of sexual metamorphosis. The syndrome is more closely related to the ratio of excretion between the 17-ketosteroids and estrogens, rather than to individual rates. The rôle of the anterior pituitary gland is uncertain.

The author is indebted to Drs. Joseph C. Aub, Charles C. Lund, Charles Lamb, Robert Fienberg, and Max Davis for referring some of the patients for this study and is especially grateful to Dr. Joseph C. Aub for helpful suggestions and to Miss Lois Towne and Miss Rita Kelley for technical assistance.

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Testosterone Propionate Pellet Absorption in the Female

[Androgens in Gynecology]

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THE CURRENT LITERATURE contains several reports on the rate of absorption of pellets of sex sterols implanted in experimental animals (1, 2). In the human being, however, only scant data are available that may furnish adequate information as to dosage and length of duration of effects of sex sterols used in this manner. No information is available as to the fate of androgenic pellets in the human female. The primary object of this article is to report our collected data on the rate of absorption of pellets of testosterone propionate implanted in patients with various gynecic disorders.

MATERIAL AND METHODS

Implantation of pellets. All implantations were made under sterile conditions in the operating room. The skin of the abdomen was prepared and then an area approximately 3 cm. in length between the pubis and umbilicus was infiltrated with 1 per cent procaine down the midline to the rectus sheath. An incision was made through the skin, subcutaneous fat and the rectus sheath was visualized. A small incision was made in the sheath exposing the rectus muscle. The pellet, or pellets, were then inserted under the sheath to lie on top of the muscle belly. The fascial sheath was closed with #1 chromic catgut and the skin and subcutaneous fat approximated by silk stay sutures. The whole procedure was frequently performed in 7 to 10 minutes. At the beginning of the study of this problem (3) the thigh was used but this site was abandoned because pain on walking frequently persisted for a few weeks.

The data on the rate of absorption were obtained by the use of pure crystalline testosterone propionate pellets that were machine-made under aseptic conditions and supplied by one manufacturer.[1] The pellets used were of two shapes, viz. cylindrical and pill-shaped, and they varied in weight from 22 to 200 mg. They were smooth, somewhat glossy in appearance and of approximately the same density. On recovery, the pellets showed slight roughening of the surface and a more or less uniform shrinkage in the original shape (fig. 1). The pellets were implanted subfascially on the muscle belly in order to assure better blood supply, more uniform rates of absorption and to lessen the tendency to be expelled spontaneously.

Sixty-seven implantations were performed on 63 patients without untoward effects. Sixty patients in this series had but one implantation of 1 to 4 pellets. One patient had three implantations and two had two implantations. A total of 123 pellets were used. Of this number, 23 pellets became available for the study of absorption rates. Fifteen pellets were removed surgically in 8 patients, thus affording an opportunity to study the rate of absorption and tissue reaction about the pellets. Eight pellets were salvaged from the 17 pellets that were spontaneously expelled in 9 patients. It is interesting to note that about 14 per cent of the pellets sloughed out. Pellets sloughed as early as 10 days and as late as 104 days. This phenomenon may have been a response on the part of the host as a reaction to a foreign body. However, faulty technic may have been responsible. This may be adduced from the fact that re-implantation in 2 patients in whom sloughing of pellets had previously occurred was not followed by a similar sequence.

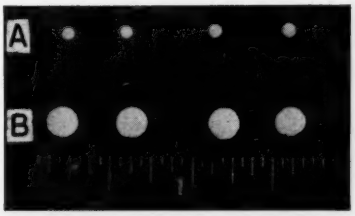

Fig. 1. *a)* FOUR SMALL PELLETS ORIGINALLY WEIGHING FROM 23–25 MG., implanted 133 days previously, (*case* 12, table 1); *b)* FOUR PELLETS ORIGINALLY WEIGHING 103 MG. EACH, implanted 175 days previously, (*case* 5, table 1).

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[1] The pellets of testosterone propionate were supplied through the courtesy of Dr. E. Oppenheimer and Dr. R. MacBrayer of Ciba Pharmaceutical Products, Inc., Summit, N. J.

TABLE 1. TESTOSTERONE PROPIONATE PELLET ABSORPTION IN THE FEMALE

Patient	Therapeutically Effective	Weight of Pellet mg.	Weight of Recovered Pellet mg.	Days in Situ	Average Absorption per Day, mg.	Diagnosis
1	Yes	200.0	142.5	56	1.03	Menorrhagia and fibromyoma
2	Yes	101.4	25.5	177	0.43	Nocturia and fibromyoma
3	Yes	101.6	43.8	84[1]	0.69	Menorrhagia, metrorrhagia
4	Yes	101.8	39.1	136	0.46	Menorrhagia and fibromyoma
5	Yes	103.0	29.6	175	0.42	Menopausal syndrome
		103.0	34.4	175	0.38	
		103.0	35.3	175	0.38	
		103.0	35.6	175	0.37	
6	Yes	101.8	49.0	104[1]	0.51	Menorrhagia and fibromyoma
7	No	102.8	50.1	170	0.31	Dysmenorrhea
		51.2	15.4	170	0.21	
8	Yes	102.2	69.5	36[1]	0.90	Dysmenorrhea
		51.8	31.8	36[1]	0.56	
		51.2	29.5	36[1]	0.60	
9	No	47.0	37.2	38	0.26	Massive fibromyoma
10	No	50.0	48.6	3	0.47	Massive fibromyoma
11[2]	No	50.0	35.3	38[1]	0.46	Menorrhagia, metrorrhagia and fibromyoma
		50.0	32.4	45[1]	0.37	
12[2]	No	23.0	5.2	133	0.13	Menorrhagia, metrorrhagia and fibromyoma
		23.4	5.4	133	0.14	
		23.6	5.7	133	0.14	
		25.0	7.7	133	0.13	
13	Yes	23.6	11.4	59[1]	0.23	Menorrhagia and fibromyoma

[1] Pellet spontaneously expelled.
[2] 11 and 12, implantation in the same patient on two different occasions.

RESULTS

Since there seemed to be no significant difference in the absorption rates of the pellets that were surgically removed and those that sloughed, the data on both are included in this report. This observation confirms a similar impression held by Howard and Jewett (4). Table 1 records the number of days the pellets remained in situ, the original weight of the pellets, the weight of the pellets recovered, and the average absorption per day. In figure 2 the percentage of absorption of 10 pellets of roughly 100 mg. each is plotted against the number of days that the pellets remained in situ. Figure 3 shows the mean curves of percentage absorption for each weight-group of pellets, i.e. five 25-mg. pellets, seven 50-mg. pellets, one 200-mg. pellet, and ten 100-mg. pellets. Note that the distribution for each group allows for a mean curve of similar character. From the graphic analysis of these absorption curves it appears that the relative absorption over a given period of time is less the larger the size and weight of the pellet although the absolute absorption is greater. This is of significance for the interpretation is clear. If pellets are manufactured under standard conditions i.e. uniformly compressed crystalline material, it holds that pellets of greater weight will be of proportionately greater size. The rate of absorption per pellet will, therefore, depend on its weight, size and surface area. The percentage of absorption of each weight group of pellets will follow its own definite curve. The total rate of absorption on any given day or at any given time depends on the number of pellets implanted and not on the actual

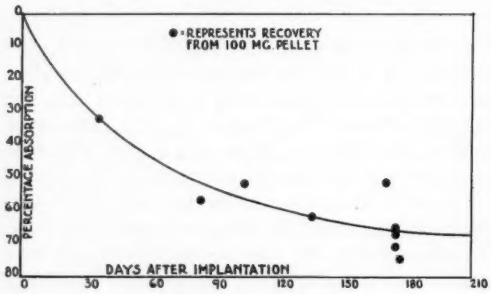

Fig. 2. PERCENTAGE MEAN ABSORPTION CURVE FOR 100 MG. PELLETS

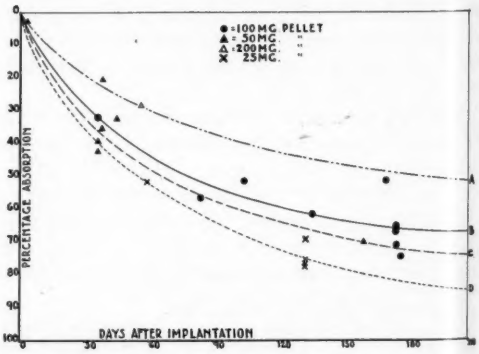

Fig. 3. PERCENTAGE MEAN ABSORPTION CURVES FOR *A*, 200 mg., *B*, 100 mg., *C*, 50 mg., *D*, 25-mg. pellets

weight of the pellets. For instance, in *case 7*, a 100 mg. and a 50-mg. pellet were implanted at one time. During the 170 days that they remained in situ, it may be said that an average of 0.520 mg. of testosterone propionate was given off per day by the two pellets. Actually, the 100-mg. pellet gave off only 50 per cent more material than the 50-mg. pellet and not twice as much as would be expected if the rate of absorption depended merely on weight. If three 50-mg. pellets had been implanted instead of the 100 and the 50-mg. pellets then the average daily absorption would probably have been about 0.63 mg. in that particular patient. In other words, 150 mg. composed of three separate 50-mg. pellets implanted at one time would have given off more particles of material at the end of 170 days than 150 mg. composed of one 100 and one 50-mg. pellet, or as much as 200 mg. composed of two 100-mg. pellets. Such an assumption is again borne out by an analysis of *case 8* in which one 100 and two 50-mg. pellets were implanted at one time. Since pellets of similar size are more or less absorbed at moderately uniform rates (see *case 5* and *case 12*) and since the rate of absorption depends on the number of pellets and their surface area we undertake to present the following hypothesis: The rate of absorption of any given amount of crystalline hormone depends on the number of pellets implanted at one time and not on the size or weight of the pellets and the time that the pellets continue to give off appreciable material depends on the size and weights of the pellets implanted.

Probably the most important factors in the rate of absorption are the surface area of the pellet exposed to the action of the body fluids, the density of the pellet, the size of the particles (crystals) and the site of implantation. Howard and Jewett found that for the first few days after pellet implantation there was a rapid absorption amounting to 3 or more milligrams per day when using 200-mg. pellets. After this they believed that capsule formation about the pellet slowed the absorption rate to somewhere between 0.5 mg. to 1.0 mg. per day (4). They implanted their pellets subcutaneously. In our series, capsule formation was an inconstant feature, probably because of the site of implantation. Forbes emphasizes that the site of implantation (e.g. intramuscular instead of subcutaneous) may considerably alter the absolute periods required for absorption of a pellet. Mark and Biskind (5) in their work on rats found that the physiological need of the animal plays no rôle in the rate of absorption since there was no significant difference in the rate of absorption of pellets implanted in either castrate or intact animals. Forbes found that the sex of rats had no differential effect on absorption rates. The values obtained by us for absorption rates of testosterone propionate pellets implanted in females were more or less in agreement with the values obtained for men by other investigators.

SUMMARY AND CONCLUSIONS

1. Pellets of testosterone propionate implanted subfascially for the therapy of certain gynecic disorders proved, with certain reservations, to be a satisfactory method of administering small amounts of the hormone over a prolonged period of time without provoking arrhenomimetic phenomena.

2. Data on the average absorption rate per day were obtained on 23 pellets in 13 instances. The number of days the pellets remained in situ varied from 3 to 177 days.

3. The weight of the pellets in this series fell into four groups: *a*), approximately 25 mg. (5 pellets); *b*), 50 mg. (7 pellets); *c*), 100 mg. (10 pellets); *d*), 200 mg. (one pellet). When the percentage of absorption was plotted against the number of days that the pellets remained in situ, the resultant curves were more or less smooth with the individual deviations of each weight-group being only moderate in extent. The percentage of absorption during the first month was relatively rapid for all four groups. The rate of absorption progressively decreased with each succeeding month, the curve tending to level after the hundredth day. The decrease in rate of absorption was inversely proportional to the absolute weight of the pellet.

4. The average daily absorption in milligrams in the case of pellets of 100 mg. for example, is at first about 1 mg. per day and then falls off gradually, reaching about 0.5 mg. by the 100th day, and about 0.35 mg. by the 170th day. Since the daily absorption follows a more or less constant curve for pellets of certain weight it should be possible to calculate the effective life of a pellet of a given weight.

5. The rate of absorption is mainly a physical phenomenon depending on the surface area exposed to the dissolving action of tissue fluids. Influencing factors are the density of the pellet, the size of the particles (crystals) that comprise the pellet, the surface area and the site of implantation.

ADDENDUM

Since the submission of this paper a 200-mg. pellet removed 112 days after implantation, showed 41.5 per cent absorption (83 mg.). If this value were plotted on fig. 3 it would fall on *curve A*, the absorption curve for 200-mg. pellets.

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17-Ketosteroid Excretion and Seminal Function[1]

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A previous report by members of our group dealt with the correlation of seminal findings and basal metabolic rates in men investigated because of presumed sterility (1). A number of individuals, including some of those previously reported and others since that time, has been investigated with regard to 17-ketosteroid levels and seminal biometric data. The present communication reports these studies.

Methods

A group of 57 males was investigated. All patients underwent medical, urologic and endocrine surveys. All had determinations of basal metabolic rates and roentgenograms of the sella turcica made. Roentgenologic studies of bone age were made when these appeared to be indicated. No therapy was given prior to these studies.

The majority of seminal specimens was secured by masturbation after 5 to 7 days of continence. As a rule, studies were initiated within 7 to 12 minutes after the specimen was obtained.

The method for seminal evaluation was essentially that of Meaker (2). This has been described in detail by one of us (3). The accepted criteria for normal seminal values were as follows: *volume*, 3 to 4 cc.; *abnormal morphology*, 20 per cent or less; *spermatozoal motility*, 80 per cent or more; *number of spermatozoa per cc.*, 60,000,000 as the lower limit; *number of spermatozoa for the entire ejaculate*, 240,000,000 as the lower limit. The seminal findings reported are those obtained during the times when 17-ketosteroid studies were being made.

Determinations of 17-ketosteroids were made on 4 to 7 consecutive 24-hour specimens of urine of each patient by the colorimetric method of Oesting (4, 5) after extraction of the urine by the method of two of us (6). The 17-ketosteroid values used in reporting our data represent the averages of daily determinations, expressed as international units of androsterone. These findings have not been correlated with bio-assays, hence no assessment of the androgenicity of the urines of these patients can be made.

Data

The ages of the 57 patients studied ranged from 15 to 49 years. Table 1 correlates 5-year age epochs with the seminal values and with the 17-ketosteroid levels of 50 of the 57 patients. Seven patients with presumed androgenic deficiency were not included in this table.

The patients studied have been grouped as follows: *a*), those with essentially normal seminal values; *b*), those with presumed androgenic deficiency; *c*), those with decreased seminal values.

Data on 11 patients with essentially normal seminal values comprise the first group. Table 2 correlates the seminal values and 17-ketosteroid levels of these 11 patients.

Data on 7 patients who had androgenic deficiencies are presented in table 3.

Data on 39 patients with decreased seminal values are presented in tables 4 to 8 inclusive.

Discussion

From the data presented, a correlation apparently exists between the age groups and the 17-ketosteroid levels. A peak in the excretion values is reached gradually between the ages of 35 and 40 years. There is a rather marked decline in values by the end of the 45th to 49th years. This trend may reflect a qualitative change in urinary 17-ketosteroids with regard to active and inactive members of the group, and may be indicative of a stabilization of the gonado-adreno-pituitary system which has been envisioned by some

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workers as being a phase in the sexual aging of the male. There is apparently no correlation between the age of the patients studied and their seminal values.

An analysis of the data permits the establishment of no clear-cut relationship between values in the patients having higher 17-ketosteroid levels and the patients having accepted standards for normalcy, as regards seminal values. It is true that the 11 patients who had essentially normal seminal values had, as a group, the highest 17-ketosteroid levels. However, when the data on these patients are subdivided (table 2) into two groups, one which has levels higher, and one which has levels lower, than the mean figure of 115 I.U., then the group having the lower 17-ketosteroid levels averages higher seminal values in every respect. The mean 17-ketosteroid level for the 50 patients, not including those with presumed androgenic deficiency, is 86 I.U. If the data on these patients are divided into two groups, *a*), those patients with 17-ketosteroid levels of 86 I.U. or higher and *b*), those patients with 17-ketosteroid levels less than 86 I.U., no significant correlations appear, although the group levels are 139 I.U. and 56 I.U., respectively.

TABLE 1. CORRELATION OF AGES IN 5-YEAR EPOCHS WITH SEMINAL VALUES AND 17-KETOSTEROID LEVELS

5-Year Age Epochs	Number of Patients	Seminal Values				Range of 17-Ketosteroid, Averages	17-Ketosteroid Level for Group
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.		
		cc.	%	%		I.U.	I.U.
15–19	1	0.5	27	70	185,000,000		24
20–24	6	3.8	27	66	123,000,000	16–128	79
25–29	14	3.9	33	62	61,000,000	18–212	83
30–34	13	4.3	29	66	121,000,000	40–182	98
35–39	8	3.8	26	55	105,250,000	34–203	116
40–44	4	2.8	22	50	98,000,000	10–145	64
45–49	4	3.1	29	71	190,300,000	21– 60	41

TABLE 2. CORRELATION OF ESSENTIALLY NORMAL SEMINAL VALUES WITH 17-KETOSTEROID LEVELS, LISTED IN ORDER OF DECREASING 17-KETOSTEROID VALUES

Patient	Age	Seminal Values				Average Daily 17-Ketosteroid
		Volume	Abnormal morphology	Motility	Spermatozoa per c.c.	
	years	cc.	%	%		I.U.
1	26	3.0	19	75	83,000,000	212
2	37	5.0	20	70	111,000,000	203
3	30	2.0	20	95	266,000,000	182
4	36	3.0	25	85	105,000,000	169
5	28	4.0	23	80	125,000,000	131
Average	31.2	3.4	21	81	138,000,000	179
6	34	5.0	14	95	165,000,000	105
7	26	5.0	14	75	70,000,000	86
8	32	4.5	22	80	90,000,000	66
9	20	3.5	20	90	243,000,000	58
10	33	5.5	20	95	235,000,000	40
11	48	2.5	18	90	157,500,000	21
Average	32.1	4.0	18	88	161,750,000	63
Grand Average	31.8	3.9	19	84	151,000,000	115

TABLE 3. CORRELATION OF SEMINAL VALUES AND 17-KETOSTEROID LEVELS OF PATIENTS WITH PRESUMED ANDROGENIC DEFICIENCY

Patient	Age	Significant Symptoms and Findings	Seminal Values				Average Daily 17-Ketosteroid
			Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years		cc.	%	%		I.U.
1	29	Testicular atrophy, bilateral	3.0			No spermatozoa seen	59
2	42	Testicular atrophy, bilateral	0.5	100	0	Total of 4 observed	59
3	42	Testicular atrophy, bilateral	1.0	20	70	100,000,000	26
4	22	Adolescent testicular failure	0.1			No spermatozoa seen	18
5	28	Cryptorchidism, bilat.	9.0	76	20	6,000,000	62
6	30	Decreased seminal values	7.5	75	51	233,000	116
7	46	Male climacteric	6.0	73	15	260,000	86
Average	34.1		3.9	49	22	15,230,000	61

TABLE 4. CORRELATION OF 10 HIGHEST 17-KETOSTEROID LEVELS WITH CORRESPONDING SEMINAL VALUES

Patient	Age	Seminal Values				Average Daily 17-Ketosteroids
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years	cc.	%	%		I.U.
1	24	2.0	21	80	95,000,000	168
2	33	6.0	31	90	245,000,000	147
3	40	4.5	25	50	177,500,000	145
4	31	3.5	50	20	40,000,000	144
5	38	7.0	28	65	92,500,000	143
6	38	3.5	41	90	160,000,000	135
7	33	5.0	24	70	95,000,000	132
8	21	4.5	24	60	110,000,000	128
9	32	2.0	43	5	40,000,000	101
10	37	1.5	18	55	160,000,000	100
Average	32.7	4.0	31	59	121,500,000	134

TABLE 5. CORRELATION OF 10 LOWEST 17-KETOSTEROID LEVELS WITH CORRESPONDING SEMINAL VALUES

Patient	Age	Seminal Values				Average Daily 17-Ketosteroids
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years	cc.	%	%		I.U.
1	40	2.0	76	2	250,000	10
2	23	1.5	16	60	67,500,000	16
3	25	1.0	83	1	2,700,000	18
4	15	0.5	27	70	185,000,000	24
5	45	2.5	41	23	2,162,500	27
6	37	4.0	51	13	86,000,000	34
7	30	7.0	30	65	30,000,000	42
8	24	3.0	41	70	170,000,000	44
9	42	5.0	27	60	80,000,000	50
10	40	1.5	36	90	135,000,000	50
Average	32.1	2.8	43	47	75,861,000	32

TABLE 6. CORRELATION OF DATA ON PATIENTS OF GROUP WITH GREATEST NUMBER OF SPERMATOZOA PER CUBIC CENTIMETER OF SEMINAL FLUID

Patient	Age	Seminal Values				Average Daily 17-Ketosteroids
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years	cc.	%	%		I.U.
1	48	4.00	30	80	335,000,000	57
2	49	3.50	27	90	267,500,000	60
3	33	6.00	31	90	245,000,000	147
4	35	6.25	25	63	232,500,000	59
5	40	4.50	25	50	177,500,000	145
6	26	6.50	12	60	132,500,000	41
7	30	5.00	18	50	130,500,000	83
8	31	3.50	33	48	129,000,000	73
9	27	6.00	32	80	110,000,000	80
10	38	7.00	28	65	92,500,000	143
Average	35.7	5.2	26	68	185,200,000	90

TABLE 7. CORRELATION OF DATA ON PATIENTS OF GROUP WITH SMALLEST NUMBER OF SPERMATOZOA PER CUBIC CENTIMETER OF SEMINAL FLUID

Patient	Age	Seminal Values				Average Daily 17-Ketosteroids
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years	cc.	%	%		I.U.
1	32	2.0	43	5	40,000,000	101
2	34	4.5	29	58	37,500,000	70
3	28	1.5	50	30	13,500,000	76
4	29	0.1	45	40	10,500,000	62
5	28	6.0	60	85	5,000,000	74
6	25	1.0	83	1	2,700,000	18
7	45	2.5	41	23	2,162,500	27
8	40	2.0	76	2	250,000	10
9	37	1.75	100	20	Total of 12 observed	88
10	28	0.75			1 Spermatozoön seen	94
Average	32.6	2.6	43	26	11,161,000	62

The lack of correlation between data on patients with higher 17-ketosteroid levels and those patients with normal seminal values is reflected also in tables 4 and 6.

There exists a general relationship between low 17-ketosteroid levels and decreased seminal values. The data in tables 3, 5 and 7 supply this evidence. This is not an unexpected finding. It is believed generally that urinary 17-ketosteroids originate in the adrenal cortex. Urinary extracts of these substances include both the unmodified compounds and those changed by testicular metabolism. Seventeen-ketosteroid determinations, then, may be indicative indirectly of the androgenic or metabolized products present. This is based upon observations that active and inactive members of the non-phenolic 17-ketosteroid group are present in urine of normal individuals in the ratio of approximately 1:1 (7–9). Hence, the patients who had decreased seminal values and low 17-ketosteroid levels probably had some degree of androgenic deficiency which was reflected in the seminal values. It has been a common working premise with us that seminal values, as a rule, afford a good index of androgenic activity, except in those patients in whom intrinsic damage or insufficiency of the seminal epithelium exists.

Some of these patients had 17-ketosteroid levels of the same low order as those associated with hypofunction of the adrenal cortex (7, 8). However, none of them presented signs or symptoms of any adrenal disease.

TABLE 8. SEMINAL VALUES AND 17-KETOSTEROID LEVELS OF 6 PATIENTS NOT INCLUDED IN FOUR PRECEDING TABLES

Patient	Age	Seminal Values				Average Daily 17-Ketosteroids
		Volume	Abnormal morphology	Motility	Spermatozoa per cc.	
	years	cc.	%	%		I.U.
1	29	6.5	34	70	90,000,000	85
2	32	3.0	40	90	79,500,000	85
3	23	4.0	16	60	67,500,000	16
4	25	5.5	26	80	49,000,000	54
5	21	8.5	40	38	45,000,000	62
6	29	4.75	35	50	42,500,000	79
Average	26.5	5.4	32	64	62,100,000	64

When the variously encountered biometric abnormalities of the spermatozoa of patients were arranged according to ages of these patients and their 17-ketosteroid levels, no significant correlations were apparent. Likewise, no correlation existed between the 17-ketosteroid levels of patients, the degree of viscosity and of turbidity of their seminal fluids, and the viability of their spermatozoa.

SUMMARY

Studies of 17-ketosteroid levels and of seminal values were made on 57 males, aged 15 to 49 years. Significant correlation apparently existed between the age of patients and the 17-ketosteroid excretion, and between the occurrence of decreased 17-ketosteroid levels and deficient seminal values. No correlation between the age of the patients and the seminal values, or between the occurrence of high 17-ketosteroid levels and normal seminal values were apparent.

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Syndrome of Nocturnal Frequency Alleviated by Testosterone Propionate[1]

[Androgens and Nocturia]

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IN WOMEN, disturbances of micturition may occur without evidence of cardio-vascular-renal disease, anatomic defects in the urinary tract or genito-urinary infection. It is admitted that psychogenic factors frequently play an important rôle in functional bladder disorders, but what has not been readily appreciated is that nocturia, urgency, and incontinence may have a hormonal basis. We wish to draw attention to a syndrome of nocturnal frequency in women who may or may not have disturbances of micturition during the day. The routine urinary findings are usually negative or of little significance. Stigmata of endocrine imbalance such as menorrhagia, dysmenorrhea, fibromyomata may be present in the premenopausal group and vasomotor disturbances or atrophic vaginitis in the menopausal group.

In March, 1941, we reported (1) before the Southeastern Surgical Congress on the palliative therapy of fibromyomata uteri by administration of chemically pure androgenic substances. Attention was brought at that time to a pertinent observation, to wit, that moderate to severe nocturia was a universal complaint of patients with massive uterine fibroids and that amelioration of this syndrome followed the subfascial implantation of pellets of testosterone propionate. The idea has gained currency that nocturia associated with fibromyomata was due to pressure on the bladder. Although this fact has been perpetuated both in textbooks and in teaching, it may well be fallacious, as subsequent facts tend to demonstrate. Frequently, in spite of but minor reduction in size of massive fibromyomata following implantation of testosterone propionate pellets, the nocturia was alleviated.

OBSERVATIONS

Sixty-three women ranging in age from 25 to 58 years had pellets of testosterone propionate[2] implanted subfascially for the treatment of various gynecic disorders. From 1 to 4 pellets were implanted at one time. The pellets varied in weight from 22 to 200 mg. Although the average dosage was about 100 mg., nevertheless as little as 25 and as much as 400 mg. was employed. These patients, except for a few recent cases, have been under observation for 6 to 21 months. Careful evaluation of complaints yielded the information that 28 of the 63 women were regularly disturbed by urgency after retiring. Only those who, with regularity, had to void two or more times per night were included in this series. Nocturia varied from 2 to 10 times per night in different individuals but as a rule the disturbance was more or less constant for the same person. Associated with nocturia there was, not infrequently, diurnal frequency and dysuria. Of the 28 patients in question, 3 were menopausal cases and 19 had fibromyomata uteri with or without menstrual irregularities. In every one of the 28 patients the nocturnal frequency was wholly or for the greater part alleviated after pellet implantation. In several, the symptoms partially or wholly recurred with complete absorption of the pellets. It might be added, however, that of the remaining 35 patients in this series without urinary disturbances, nocturia developed in three following pellet implantation.

Electrolyte metabolism. In an effort to learn the reason for the alleviation of the nocturnal frequency, repeated blood chemistry determinations were performed on many of the patients to detect possible changes in electrolyte metabolism. Blood sodium, potassium, calcium, along with sugar, NPN, uric acid and creatinine determinations were made. The values obtained were within the limits of normal.

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[1] This work was aided by a grant-in-aid of research to the University of Georgia School of Medicine by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

[2] The pellets of testosterone propionate used in this study were furnished by Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and our thanks are due Dr. E. Oppenheimer and Dr. R. MacBrayer for their cooperation and suggestions.

Water balance. Water intake and output before and after pellet implantation was measured in but few patients. This procedure did not prove to be practical because of the need for long hospitalization. Many patients volunteered the information that they drank water much more freely before pellet implantation and that the desire for water was much lessened after this procedure. It may be, then, that alleviation of nocturnal frequency may be due not to water retention but to the effect of the steroid on pituitary activity in correcting a subclinical or mild diabetes insipidus.

Cystometric studies. Occasional cystometric studies were done. One patient who complained chiefly of nocturia, had cystometric studies before and after pellet implantation. Coincident with the clinical improvement, the cystometric studies revealed greater bladder capacity as well as greater tolerance of bladder pressure.

CASE REPORTS

L. L., aged 35, an obese colored female, complained of marked nocturia. Although she was disturbed every 15 to 30 minutes during the night, she had no disturbances of micturition during the day. She drank water rather freely. Routine urine analysis revealed nothing unusual. Cystometric studies revealed that she could tolerate a bladder pressure of 22 mm. of mercury and a maximum capacity of 400 cc. of water. Pelvic examination revealed a fibromyoma of the uterus which extended above the level of the umbilicus. Her menstrual periods were regular, of 4 days' duration with moderate pain on the first day. On Oct. 18, 1941, a pellet of 104 mg. of testosterone propionate was implanted subfascially. There was an immediate amelioration of the urinary symptoms and only occasionally was she disturbed so much as once per night. Two months after pellet implantation she volunteered the information that her fluid intake was now greatly reduced because of a slackening of her desire for water. Later on there was a gradual return to increased fluid intake but without any recurrence of nocturia. The menstrual cycle was in no way disturbed and the dysmenorrhea was but slightly alleviated. On April 9, 1942, she was submitted to laparotomy. The fibromyoma had decreased somewhat in size, for just previous to operation the tumor could be palpated one inch below the level of the umbilicus. During the 6-month period that she was under observation the blood pressure remained constant. Her weight increased from 231 to 243 lb. Libido began to increase considerably about 5 weeks after pellet implantation and began to subside just before operation. No evidence of virilization occurred. The pellet was recovered at the time of laparotomy and 80 mg. was absorbed over a period of 177 days. Cystometric studies ust prior to operation revealed an improvement in bladder capacity which was up to 650 cc. and a tolerance of bladder pressure of 50 mm. of mercury. The remarkable improvement in the nocturnal frequency which persisted throughout the period of observation must be attributed to the testosterone propionate.

A. J., a colored female, age 36, complained of a mass in her abdomen, hypermenorrhea, severe dysmenorrhea, and a nocturia of 10 to 20 times per night. Examination revealed a large fibromyoma extending 4 cm. above the umbilicus. Two pellets totalling 150 mg. of testosterone propionate were implanted subfascially on July 28, 1941. The menstrual periods that followed were regular, painless and the flow was reduced to 4 to 5 days. The nocturia which had been present for 5 years completely subsided within 2 weeks after pellet implantation. Libido which had been good before pellet implantation became very good and her sense of well being improved. The blood pressure remained more or less constant and there was a weight increase from 183 to 195 lb. There was no evidence of virilization during the 8 months she was under observation. Routine urine analyses were negative and blood chemistry determinations were within the limits of normal. About 6 months after pellet implantation there was a moderate recurrence of the excessive bleeding and the dysmenorrhea but the symptoms of polyuria and nocturia remained in complete abeyance. On March 13, 1942, a total hysterectomy was done. The pathologist reported multiple interstitial and subserous fibromyoma up to 11 cm. in diameter. The remarkable alleviation of the nocturnal frequency in this patient must be attributed to the testosterone propionate.

M. L. P., a white female 28 years old, complained of hypermenorrhea, severe dysmenorrhea, nocturia of 6 to 10 times per night and frequency during the day of 5 to 6 times. The bladder disorder had been more or less persistent for the past 5 years. She had a desire to drink quantities of water. Prior and subsequent to implantation of two 200-mg. pellets of testosterone propionate fluid intake and output studies were done. Soon after the implantation, nocturia decreased to once per night and soon thereafter to only once in every few nights. The frequency during the day was alleviated. Thus far, the menstrual cycle has remained regular, the flow normal and painless. Libido, which had been negligible prior to pellet implantation improved so remarkably that she again fell in love with her husband. She claimed that she felt more maternal and her sense of well being had improved. No evidence of virilization developed during the period of observation. The patient still drinks lots of water but not as much as before pellet implantation. Her weight has increased from 138 to 140 lb. Urine analyses before and after implantation were negative and blood chemistry studies (sugar, NPN, uric acid, creatinine, Na, K, Ca) repeated at weekly intervals have remained within the range of normal. The complete alleviation of the urinary symptoms must be attributed to the effect of testosterone propionate.

DISCUSSION

In the experimental animal (rat) high dosages of estrogen cause water retention (2). Such antidiuretic effect is characteristic not only of estrogens but also of other physiologically active steroid hormones such as androgens and progesterone (3). In the human being it may well be that estrogens and testosterone are antidiuretic and this may account for the alleviation of frequency and nocturia. However, we have

not been convinced that progesterone has similar properties. In fact, in patients in whom pellets of progesterone have been implanted (150–300 mg.) no consistent results, insofar as an increase or decrease of the symptoms of frequency and nocturia have been observed (4). Selye believes that in the experimental animal (rat) progesterone and desoxycorticosterone are diuretic and thus differ in their action from that of testosterone. In human beings crystalline testosterone propionate pellets implanted subfascially proved diuretic in only 3 of the 35 patients who did not have disorders of micturition and was antidiuretic in all of the 28 patients who did have nocturia, with or without diurnal distress. We also found that moderately large doses of testosterone propionate (25 mg.) administered parenterally at 4 to 7 day intervals were successful in diminishing the severity of urinary distress in several menopausal patients. Mocquot and Moricard (5) were the first to note that functional disorders of micturition in menopausal women could be ameliorated by testosterone. Small doses of testosterone propionate (5 to 10 mg.) have been used in the alleviation of premenstrual edema when associated with premenstrual tension (6). Small doses of progesterone may likewise be used. It appears that small doses of these steroids may have mild diuretic properties, although this point has not been substantiated. Recently a young surgically castrate female of 26 years of age complained of vasomotor disturbances, dysuria, urgency and marked nocturnal frequency. She had an intractable trichomonas vaginalis which had been incriminated as responsible for the genito-urinary complaints. Thirty mg. of estradiol[3] and 150 mg. of progesterone[3] were implanted subfascially. The vasomotor flushes were gradually alleviated; the relief of the urinary symptoms, however, was immediate and dramatic in spite of the persistence of the trichomonas vaginalis. A few months later spontaneous extrusion of the pellets occurred with subsequent recurrence of the urinary disturbance.

There are many indications that the genito-urinary tract is probably under hormonal influence. This may be adduced from the following facts: *a*), In pregnancy, hypertrophy of the ureters, hydronephrosis and other genito-urinary disturbances readily occur. *b*), In the climacteric, urinary symptoms attributable to an estrogen deficit such as urinary frequency, urgency and incontinence, are common accompaniments of the menopausal syndrome. These symptoms, according to Salmon et al. (7), are usually refractory to orthodox treatment and all but few patients may be kept symptom-free on a maintenance dose of estrogens. *c*), Certain components of the genito-urinary system are under hormonal influence. Korenchevsky and his colleagues (8) have long known that androgens were nephrotrophic causing increase in weight of kidneys and in size of tubules in both normal and castrate female rats.

It has been observed in the mouse, that males always have considerably larger kidneys than females of the same size. Castration in males reduces the size of the kidney to the female level, while ovariectomy exerts no significant effect on the female kidney. Selye (9) has shown that testosterone does not merely increase the size of the kidney of the mouse but actually protects the tubular cells against the damaging effect of sublimate. This protective action of testosterone is evident in both sexes but is somewhat more marked in female than in male mice. Furthermore, Selye and Friedman (10) have shown by experiments on the mouse that renal atrophy which usually develops subsequent to the hydronephrosis caused by ligature of the ureter may be inhibited and delayed by testosterone administration. Selye (11) believes that testosterone exerts a specific action on kidney tissue and histologically such kidneys are characterized by pronounced hypertrophy of the epithelium of the proximal and distal convoluted tubules and of the epithelium lining the parietal lamina of Bowman's capsules. Albert (12), working in Selye's laboratory, has recently shown that in the rat the enlargement of the pituitary and adrenals caused by estradiol could be inhibited by testosterone; the renotrophic action of testosterone, however, could not be prevented by simultaneous injections of estradiol.

CONCLUSIONS

1. Among the frequent causes of nocturia there may be listed cardiovascular-renal disease, anatomic defects in the urinary tract, genito-urinary infections and psychogenic factors. A common causative factor heretofore not readily appreciated is the hormonal basis for nocturnal frequency.

2. In a series of 63 women in whom 1 to 4 pellets of testosterone propionate were implanted subfascially for various gynecic disorders, it was noted that 28 of them suffered from nocturnal frequency. Although 19 of the 28 women with this syndrome had fibromyomata uteri, the nocturia nevertheless was wholly or partially alleviated in all of them following the implantation. For this reason it is felt that the belief perpetuated in textbooks and teaching may well be fallacious—that nocturia associated with fibromyomata is due to pressure on the bladder.

3. Nocturia and diurnal distress for which no pathologic basis can be ascertained often prove refrac-

[3] Estradiol and progesterone pellets were supplied through the courtesy of Dr. W. H. Stoner of the Schering Corporation, Bloomfield, New Jersey.

tive to orthodox methods of treatment. Before contemplating surgery for the relief of this syndrome it is well to reconsider the rôle played by such factors as fibromyomata or a markedly anteflexed mobile uterus pressing unduly on the bladder or certain anatomic defects of the bladder such as mild cystocele or urethrocele. The frequency of bladder discomfort incident to these factors has been overstressed. The common tendency to operate upon such cases appears unwarranted before an ample course of estrogens or androgens has first been tried.

4. Evidence has accumulated that the physiologic processes of the genito-urinary tract may be influenced by various hormones. Androgens are nephrotrophic. Testosterone exerts a specific action on kidney tissue. The reasons for the amelioration of certain disorders of micturition following steroid therapy may be a direct sequence to hormonal action either on kidney function, bladder tone, pituitary activity, water balance, electrolyte metabolism or some other mechanism at present not understood.

5. As a result of our experience, we may say that sterile crystalline testosterone propionate pellets implanted subfascially will ameliorate the syndrome of nocturnal frequency herein described. From 25 to 400 mg. may well be used without fear of arrhenomimetic phenomena.

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Testosterone Propionate in the Treatment of Angina Pectoris

[Angina Pectoris]

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Extensive experimentation in animals has demonstrated that the sex hormones very definitely effect certain non-sex organs of their bodies. Ratschow and Kosterman (1), using androgens experimentally in rats, report an absence of sloughing following severe vasoconstriction by ergotamine. Korenchevsky (2) and his coworkers report changes in weight and in histologic structure in rat livers and hearts following administration of androsterone or testosterone esters to the animals, attributing certain hepatotrophic and cardiotrophic properties to these hormones. That these hormones also exert nephrotrophic effects was reported in an earlier paper by the same authors. Therapeutic applicability of these properties suggests itself in disorders of these organs in human beings and it is the purpose of this report to describe the results of such treatment in suitable cases of angina pectoris and of angina of effort.[1]

The effect of testosterone on the human cardiovascular system has been the subject of but few reports in the literature thus far. Walker (3) reported symptomatic improvement in peripheral circulation following testosterone administration in 6 cases, and Edwards, Hamilton, and Duntley (4) report an increase in arterialization after treatment with testosterone propionate in 7 male patients, 3 suffering from thromboangiitis obliterans and 4 from artiosclerosis. Studying the effects of testosterone on metabolism, Jones, McCullagh, McCullagh, and Buckaloo (5) report an increased basal metabolic rate in 11 patients studied and, moreover, an increase or decrease in velocity of blood flow paralleling rise or fall in basal metabolic rate as influenced by testosterone. Reports thus far are conflicting with regard to the effect of testosterone on blood pressure although there are indications that certain cases of hypertension may be favorably influenced (6). Among clinical studies of the effectiveness of the hormones in cases of angina pectoris *per se* is that reported by Lesser (7). This investigator administered testosterone propionate to 24 patients with angina pectoris in order to determine its influence on the frequency and/or severity of attacks. Depending upon severity of symptoms and response to treatment, the dosage schedule employed was 25 mg. every 2 to 5 days for a total of 5 to 25 injections. All patients improved as measured by diminution in frequency, duration, and severity of their anginal attacks and by their ability to increase physical activity without precipitating attacks. This improvement persisted for 2 to 12 months following interruption of therapy. Similar results did not follow injections of sterile sesame oil given as a control measure.

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[1] The testosterone propionate (Neo-Hombreol) used in this study was supplied by Roche-Organon, Inc., Nutley, N. J., through courtesy of M. C. James, M.D.

CASE REPORTS

All cases herein reported presented a typical history and a clinical picture of angina pectoris or of substernal pain on effort. Most of these patients carried nitroglycerine to relieve attacks. The basal metabolic rate was abnormally low in each. Prior to treatment with testosterone propionate, one patient had been unable to walk a distance of one-half of a city block after lunch for the past 5 years without precipitating an attack. In 3 cases the blood pressure was 150 mm. Hg systolic or more; in all 3 cases it came down to 130 mm. Hg or less following the administration of testosterone propionate. The general appearance of the skin changed from a sallow to a more natural pinkish tone and all of the patients expressed a feeling of euphoria. Three had headaches in the late afternoon which disappeared after the second and third injection. An increased endurance, mental agility and ambition was apparent to the patients as well as to their friends. Not one has had a return of angina or even distress since treatment began.

P.H. Age 75. For 5 years he had been experiencing difficulty in breathing while walking and suffered sharp pains in the precordial region concomitantly. Nitroglycerine tablets relieved the pain. He was unable to walk half a block after lunch without an attack. His B.M.R. was minus 18, pulse 60 at rest, temperature 97.6° F., blood pressure 100 over 70 mm. Hg. Thyroid medication seemed to increase the pain. Starting in February, 1941, he was

given 25 mg. of testosterone propionate 3 times a week, continuing for 2 months. After the second injection he was able to walk 3 blocks without any discomfort. The number of injections was decreased to 2 a week and later to 1; for the past 3 months one 25 mg. injection per month has sufficed. His color, which was of a grayish hue, is now a healthy pink. Blood pressure is now 120 over 80 mm. Hg, pulse 72 at rest, temperature 98° F. He walks 4 or 5 blocks a day without discomfort and states that his mental and physical endurance have increased to a marked extent.

W.C. Age 54. For 6 years he has had substernal pain on effort, definitely diagnosed in his case as a manifestation of coronary artery disease. His color was sallow and he appeared very much older than his years. Blood pressure was 160 over 94 mm. Hg, pulse 62 at rest, temperature 98° F. B.M.R. was minus 15. He had been taking 5 grains of thyroid a day. He was very tired and lacked energy to complete his usual day's work. Treatment was started with 25 mg. of testosterone propionate 3 times a week; thyroid medication was stopped at this point. During the second week he was able to walk 5 blocks during a very cold day without precordial discomfort. He had more energy and could work a full day without tiring. After one month his color improved and he appeared much younger than when he started to take the injections. During the past 3 months he has been taking one injection of 25 mg. a month and has had no return of anginal symptoms. His endurance has increased and he is able to climb two flights of stairs with ease.

E.D.L. Age 52. Has had angina pectoris for the past 7 years, the attacks being precipitated by effort. The electrocardiogram, as in the other cases, revealed no myocardial change. In addition to the anginal syndrome he had severe headaches in the late afternoon, and was ready for bed at 8 o'clock every night. Twenty-five mg. of testosterone propionate was given 3 times a week for 1 month. Headache was relieved after the second injection and anginal symptoms disappeared after the fourth. The frequency of injections was gradually reduced to 1 a month. He is less fatigued after physical and mental effort and able to climb 3 flights of stairs without discomfort.

C.D. Age 60. Has had anginal symptoms for the past 3 years and has been unable to walk more than a block without substernal pain. Nitroglycerine tablets relieved pain. The pulse was 70, blood pressure 110 over 70 mm. Hg. Twenty-five mg. of testosterone propionate was given 3 times a week for 1 month. After the third injection anginal symptoms disappeared, and he was able to walk several blocks without distress. At the end of 3 weeks his pulse was 72, blood pressure 120 over 80 mm. Hg. There has been a decided improvement in mental and physical endurance and he has been free of substernal pain for 11 months.

M.A.P. Age 67. For more than a year he had experienced pain in his chest on walking up a slight hill on his way home. Angina pectoris was diagnosed and nitroglycerine prescribed. Physical examination was negative except for a blood pressure of 160 over 92 mm. Hg. He would have 5 or 6 attacks during the day and even walking on level ground for more than one block would bring on precordial distress. He was given 25 mg. of testosterone propionate 3 times a week for 6 weeks. After the sixth injection he said he had no discomfort on walking up the hill to his home. Treatment was continued for several months longer, employing the same dosage schedule, but it was later decreased to two injections a month and later to one. He is now able to walk up two flights of stairs and several city blocks without return of anginal symptoms. His blood pressure is now 140 over 82 mm. Hg.

C.T.E. Age 61. Has had angina pectoris for 3 years and always carried nitroglycerine tablets for relief of pain. He was unable to go up stairs without an attack and would have 3 and 4 'spells' a day. Physical examination showed a man older than his years, blood pressure 100 over 70 mm. Hg, pulse 65, temperature 98° F. Testosterone propionate was given in 25 mg. doses 3 times a week for 3 weeks. It was then reduced to twice a week and later to once a month. After the sixth injection he had no further anginal symptoms and could walk up two flights of stairs or four blocks, even in cold weather without a return of precordial distress. He has now been free from pain on effort for 6 months. Blood pressure is 116 over 74 mm. Hg, pulse 70.

H.C.E. Age 66. Complained of pain in substernal region on effort and was unable to walk two blocks or climb one flight of stairs without discomfort. He complained, also, of cold hands and feet and lack of energy. Twenty-five mg. of testosterone propionate was given 3 times a week for 6 weeks. After the sixth injection he was able to climb three flights of stairs and walk five blocks without precordial discomfort. Treatment was reduced to one injection a month and 5 mg. of methyl testosterone orally a day. No anginal symptoms have been present for the past 11 months.

COMMENT

Upon analyzing these case reports it will be seen that 7 patients ranging in age from 52 to 75 years who presented the clinical syndrome of angina pectoris or substernal pain on effort, were treated with testosterone propionate; 25 mg. of this substance was injected intramuscularly 3 times a week for 6 to 8 weeks and was then gradually reduced to this amount once a month. The average number of injections covering a 12-month period was 30, while the average number of injections before improvement was apparent was 4.

No unfavorable effects were observed in any of the cases. On the contrary, a general improvement in mental and physical endurance was noted in all cases. Relief from angina pectoris was obtained in each case and in none has there been any return of precordial or substernal pain, even after walking several blocks and climbing two or more flights of stairs. This symptom-free state has obtained for 6 months in some cases, and for 11½ in others.

Purely scientific study of these case reports at once

raises the objection that the value of the therapy has been judged largely upon the basis of subjective improvement. But while it is true that this objection is perhaps too often a valid one when some new therapy is reported as being highly successful in this or that disorder, the special nature of the subjective symptoms in these cases of angina pectoris renders them capable of being viewed in an objective light. It is well known how varied may be the responsiveness to the same degree of pain in different patients, but the pain of coronary occlusion is classic in its intensity and there is little doubt that the most stoic patient, gives creditable clinical information when he says that he did or he did not have this pain. Again, each of these patients reported a general improvement in mental and physical endurance and in a sense of well-being—all factors more or less subject to personal interpretation. Yet these same improvements are reported by practically every hypogonadal patient who has ever received replacement therapy with the indicated hormone and in view of this fact the stigma of subjectiveness which attaches to these observations becomes less marked. As for objective findings by which results could be judged, observable and measurable improvements in blood pressure, basal metabolic rate and skin color occurred. Of great practical importance along this line of thought is the fact that Lesser (7) substituted sesame oil for testosterone propionate, using many different variants of procedure, and was in no respect able to duplicate the results he obtained with the hormone in his cases of angina pectoris. There remain now to be considered the mechanism by which testosterone exerts its salutary influence upon these cases and the rationale of its therapeutic use in coronary artery disease.

Rôle of the sex hormones in coronary occlusion. The pain of angina pectoris or of coronary thrombosis, syndromes which are but manifestations of different degrees and types of coronary artery occlusion, is explained on the basis of myocardial ischemia arising out of the simple fact that the supply of blood to the heart muscle is grossly inadequate to the demand at a given moment. Years of painstaking research have still failed to reveal the exact mechanism of that inadequacy, but atheromatous changes in the coronary intima resulting in narrowing of the lumen or, in the absence of arterial pathology, abnormal vasomotor response are thought to be causative factors. With regard to the latter of these, it is not difficult to conceive of sluggish, inadequate, or absent dilatory powers on the one hand or of excessive vasoconstriction on the other. Probably both phenomena, atheromatous narrowing and vasomotor instability, are etiologically concerned in some cases. But whatever the mechanism, inadequate coronary circulation is at fault and therapy must be directed at its improvement, and production of vasodilation and/or promotion of collateral coronary circulation are the obvious means of affecting such improvement.

Vasodilator properties of the sex hormones. There is much experimental and clinical evidence in support of the contention that estrogens and androgens in some manner cause vasodilation. This evidence is reviewed by Bonnell, Pritchett, and Rardin (8) whose excellent paper on the use of the sex hormones in the treatment of angina pectoris and coronary artery disease is drawn upon at this point. These authors cite Reynolds and Foster (9) who observed dilatation of vessels in the ears of rabbits following estrogen administration. Sympatheticotropic properties have also been ascribed to these substances in that dilatation of the pupil is produced by their action. Bonnell et al. further cite authorities for the following concepts: *a*), that estrogens exert a dilating action on the small vessels distal to arterioles. *b*), That estrogens are pharmacologically cholinergic, that therefore they act peripherally through enhanced acetylcholine activity, and that this same mechanism may be concerned in producing coronary dilatation. *c*), That estrogen deficiency in certain women produces changes in the coronary arteries and myocardium which can be corrected by estrogen replacement therapy but not by rest or by vasodilating drugs. The suggestion is advanced by Bonnell et al. that "a deficiency in gonadal hormone, or an endocrine imbalance in certain individuals possessing an autonomic nervous system capable of an abnormal response, is the factor which leads to functional or organic changes in the vascular system during or after the climacteric period of life."

Rôle of sex hormones in promoting collateral circulation. Whether or not testosterone promotes development of coronary collateral circulation cannot be definitely stated but Lesser (7) speculates about this question in connection with the improvement noted in his cases of angina pectoris following their treatment with the hormone. Lesser cites authorities for the observations that anastomotic channels between the major coronary arteries develop to an increasing degree with advancing age, that the development of these channels depends upon partial or complete occlusion in one or more of the larger coronary arteries, and that the collateral circulation thus developed is in some cases entirely adequate.

Relationship of the climacteric periods of life, coronary artery disease and sex hormone therapy. Although no studies have been conducted on the basis of which declining gonadal hormonal function, conceded by all to be the cause of the menopause in women and by many to be the cause of a somewhat similar phenomenon in men, can be either proved or disproved as being etiologically involved in coronary

artery disease, certain facts become particularly interesting when viewed in the light of this problem. For example, it is significant to note the ages of the patients with angina pectoris reportedly benefited by testosterone, keeping in mind the age groups in which climacteric symptoms as well as those of coronary occlusion most frequently manifest themselves. Bonnell et al. noted clinical improvement in 22 of 23 patients with coronary artery disease after treating them with sex hormones. Angina pectoris had been definitely diagnosed in 21 of these patients. The group was composed of 18 men and 5 women and ages varied from 42 to 78 years, although 47 to 60 years is a more accurate representation of ages since 17 of the patients were within this age group. The 7 patients herein reported ranged in age from 52 to 75 years.

Also worthy of note is the presence or absence of associated climacteric symptoms in these patients whose chief complaints were referable to the heart. Such symptoms were present in 4 of the 5 female cases reported by Bonnell; they were present in only 3 of the 18 male cases. The 7 cases herein reported were all males and all had concomitant climacteric symptoms.

At the present time the most that can be said is that cases of angina pectoris often occur in patients whose output of sex hormone is deficient as evidenced by their exhibiting the climacteric syndrome and that sex hormone replacement therapy appears to be efficacious in the treatment of both phenomena. By virtue of its having been reported in hundreds upon hundreds of cases the subjective finding, 'improved sense of wellbeing,' takes on the clinical importance of an objective result in evaluating the efficacy of testosterone therapy in male climacteric cases. To be considered, therefore, is the possibility that this sense of wellbeing is at least a contributory factor to improvement in angina pectoris in that morbid anxiety, great emotional stress and the like are less apt to figure as precipitating causes in the attacks, and, also, in that the general tonic properties of testosterone which have been at least partly concerned in that improved sense of wellbeing have brought about an improved bodily economy which in itself militates against attacks of coronary pain. It has been suggested that the increased circulation time and the incease in basal metabolic rate caused by testosterone results in an improved vascular tone in the coronary arteries as well as in all other vessels and Steinach, Peczenik, and Kun (6) believe that the beneficial action of the sex hormones on blood circulation in true male hormone deficiency cases is due to their exerting a nonspecific influence upon the blood vessels via the central nervous system.

SUMMARY AND CONCLUSIONS

1. The beneficial results of androgen therapy in 7 cases of cardiac angina are described.

2. The effect of sex hormones upon the circulatory system and especially upon coronary circulation is discussed and the clinical investigations of others upon this subject is reviewed.

3. The frequent coexistence of coronary artery disease and the climacteric syndrome is remarked upon, directing attention to the possibility that they are both manifestations of hypogonadism.

4. Testosterone propionate appears to be a valuable therapeutic agent in angina pectoris, the effect of the hormone being mediated through its vasodilating properties acting upon the coronary circulation and/or through development of coronary collateral circulation.

5. The undesirability of unduly stimulating the libido in patients in whom vascular accidents might be precipitated is obvious. However, this should be no deterrent to sex hormone therapy provided careful selection of patients and control over dosage is practiced.

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Some Metabolic Effects of Testosterone Implants

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THORN AND HARROP (1) have shown that the administration of testosterone to normal dogs is followed by a decreased excretion of sodium and water, an effect resembling that of adrenal cortical extract. Kochakian and Murlin (2) found the nitrogen content of urine in castrate dogs diminished after the injection of androgens, while Thorn and Engel (3) noted a decrease in urinary nitrogen in normal dogs given testosterone propionate. These reports represent but a few of the recorded observations on animals.

More recently, Kenyon et al. (4) have shown that in normal men and women, and particularly in eunuchoids, the injection of testosterone propionate 'produced a reduction in the urinary excretion of nitrogen, sodium, potassium and chloride.' When the injections of testosterone were discontinued, the excretion rates returned to the pre-injection levels. Jones et al. (5) noted that the oral administration of methyl testosterone possessed 'the property of causing nitrogen, electrolyte and water retention.' The reported observations, however, have been made over comparatively short periods of time (up to 14 days), injections being given daily or twice daily.[1]

Since Ornstein and one of us (6) have shown that the implantation of testosterone pellets is followed by a satisfactory clinical response lasting for 2 to 5 months, it appeared important to determine if the 'life' of a pellet may be determined by such metabolic criteria. Two such studies over a longer period of time are now reported.

CASE REPORT

Case 1. N. B., male, age 21 years, was first seen on Oct. 29, 1940. The past history revealed mumps in infancy, a mastoidectomy at 6 years of age, a bilateral herniotomy at 12 and an operation for recurrent hernia at 19 years. At 16 years of age, several injections of an unknown endocrine preparation were administered for undescended testes and at 19 years, he received 50 injections of an anterior pituitary-like preparation. The operations and injections were of no avail. His chief complaints were feminine appearance, very small genitalia, undescended testes, lack of facial and body hair and high pitched voice. He seldom had erections, libido was slight and attempts at coitus were unsatisfactory. His appearance was that of the classical eunuchoid; the lower half measurement (superior symphysis pubis to heel) was 37 inches and the upper half measurement (superior symphysis pubis to vertex) was 29 inches. The height was 66 inches, span 72.5 inches and weight 161 pounds. His appearance was feminine, the complexion smooth and the cheeks were pink. The penis was minute and hypospadias was present. There was a slight amount of pubic hair with feminine distribution. The testes were impalpable and the scrotum was small and shrunken. The visual fields were normal. Radiographs revealed a normal sella turcica but there was evidence of delay in epiphyseal ossification. The blood pressure was 132/98 mm. Hg. Otherwise, the physical examination was negative.

EXPERIMENT AND RESULTS

A diet containing 200 gm. of carbohydrate, 75 of protein, 100 of fat and 2.0 to 2.5 of sodium chloride was given daily throughout the investigation. During each period of observation, the subject was hospitalized for at least 6 days; urine voided on the last 3 or 4 days was collected in 24-hour lots and analyzed for total nitrogen by a micro-Kjeldahl procedure (7), for chlorides by the Volhard-Harvey method (8), for phosphates by the uranium acetate procedure (9) and for creatinine by the method of Folin (10).

After adequate control studies were made, the patient received, intramuscularly, 50 mg. of testosterone propionate[2] daily for 5 days and on the 6th day, 450 mg. of testosterone,[2] subcutaneously implanted. Subsequent studies were made at approximately monthly intervals for 5 months. The detailed results are given in table 1. Figure 1 demonstrates graphically

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[1] Since this paper was written, Sandiford, Knowlton and Kenyon (*J. Clinical Endocrinology* 1: 931. 1941) studied the urinary nitrogen in a eunuchoid who received intramuscularly testosterone propionate in doses of 5 to 50 mg. daily for 2 months. Throughout the entire period, the urinary nitrogen remained depressed.

[2] Testosterone propionate (Oreton) and the testosterone pellets were supplied through the kindness of Dr. Max Gilbert, Schering Corp., Bloomfield, N. J.

TABLE 1. URINARY EXCRETION OF NITROGEN, CHLORIDES AND PHOSPHATES IN A 23-YEAR-OLD EUNUCHOID BEFORE AND AFTER INJECTION OF OF 250 MG. OF TESTOSTERONE PROPIONATE AND IMPLANTATION OF 450 MG. OF TESTOSTERONE

Date	Urine Volume cc.	Nitrogen		Chlorides		Phosphates		Creatinine		Remarks
		gm./24 hr.	Average	gm./24 hr.	Average	gm./24 hr.	Average	gm./24 hr.	Average	
November 25	1975	13.7		3.8		2.7		2.0		
26	2450	13.6		2.5		2.5		2.0		
27	2175	14.3	13.8	4.8	3.7	2.5	2.6	2.0	2.0	
28	1750	9.9		1.4		2.1		1.6		50 mg. of testosterone propionate intramuscularly on Nov. 28, 29 and 30.
29	2105	11.1		2.1		2.9		1.3		
30	1585	11.2	10.7	1.9	1.8	2.6	2.5	1.7	1.5	
December 1	1600	7.1		1.6		1.6		1.5		50 mg. of testosterone propionate intramuscularly on Dec. 1, 2. 450 mg. of testosterone implated on Dec. 3.
2	1555	8.1		1.2		1.7		1.8		
3	1400	7.9		1.7		1.7		1.7		
4	1600	9.6	9.2	1.6	1.6	2.4	2.1	1.7	1.6	
30	2560	5.5		2.6		1.2		1.8		
31	2600	9.4		2.6		2.1		2.5		
January 1	2050	6.8		2.1		1.4		1.7		
2	2420	7.9	7.4	2.9	2.5	2.3	1.8	2.5	2.1	
February 15	2575	10.0		2.8		1.8		1.9		
16	2300	8.9		2.5		1.4		1.3		
17	2700	12.0	10.2	2.2	2.5	4.0	2.4	1.9	1.7	
March 28	2425	13.2		3.9		3.1		1.8		
29	2120	9.4	11.3	3.9	3.9	2.3	2.7	1.3	1.6	
May 23	1950	9.7		5.4		3.1		2.2		
24	1600	12.1		2.5		2.9		2.1		
25	2460	13.1	11.6	2.0	3.3	2.9	3.0	2.5	2.2	
June 28	1860	12.7		4.3		3.9		2.2		
29	1660	12.9		3.3		3.6		2.2		
30	2200	12.0	12.5	4.8	4.1	3.6	3.7	2.6	2.3	

the average values obtained and shows that the period of symptomatic effect of the testosterone implant (as gauged by an increase in erections and libido) parallels closely the period in which the urinary excretion of nitrogen, chlorides, and phosphates was diminished.

The clinical response to testosterone was dramatic. Approximately three months after the implantation, some 'testosterone withdrawal' symptoms appeared which became more pronounced at the fourth month. One month later, there was a slight return of 'testosterone effect' which, however, was accompanied by no pronounced diminution in the urinary excretion of the various components studied.

TABLE 2. URINARY EXCRETION OF NITROGEN, CHLORIDES AND PHOSPHATES IN A 28-YEAR-OLD EUNOCHOID BEFORE AND AFTER THE IMPLANTATION OF 450 MG. OF TESTOSTERONE

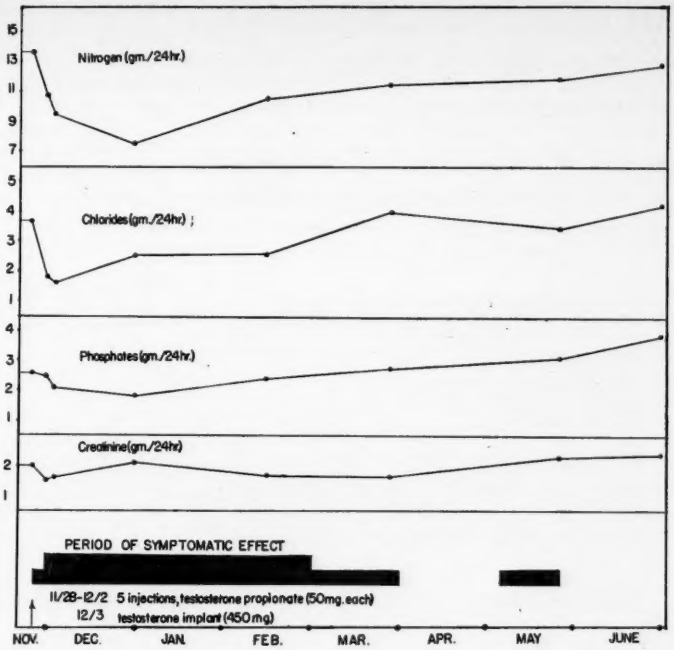
Date	Urine Volume cc.	Nitrogen		Chlorides		Phosphates		Creatinine	
		gm./24 hr.	Average	gm./24 hr.	Average	gm./24 hr.	Average	gm./24 hr.	Average
June 26	1380	10.3		9.0		3.1		2.9	
27	1160	10.0		7.4		2.8		2.9	
28	1150	10.4		4.8		2.6		2.6	
29	1240	10.0		4.0		3.1		3.1	
30	1650	12.4	10.6	4.6	5.9	3.2	2.9	3.2	2.9
July 1	*450 mg. of testosterone implanted*								
28	1800	9.6		3.1		1.8		2.8	
29	1600	8.2		4.2		2.1		2.6	
30	1960	10.0	9.2	5.6	4.3	2.2	2.0	3.2	2.8
Sept. 1	1250	8.1		4.0		2.6		2.9	
2	1540	7.2		5.6		2.8		2.8	
3	1400	7.7	7.6	5.6	5.0	2.7	2.7	2.9	2.8
Oct. 7	600	8.8		5.4		2.2		2.6	
8	1150	9.9		6.2		2.3		2.2	
9	1090	9.3	9.3	6.1	5.9	2.5	2.3	2.8	2.5

CASE REPORT

Case 2, A. R., male, age 28 years, was first seen on June 13, 1941. The chief complaints were failure of genital development and absence of libido. The past history revealed migraine headaches for years accompanied by blurred vision, hot and cold sensations and nausea. Recurrent episodes of alternating diarrhea and constipation had occurred since 1938. One year ago, he sustained a fracture of the pelvis in an automobile accident. The physical examination revealed an infantile penis, impalpable testes and no facial but scanty axillary and pubic hair. The blood pressure was 130/80 mm. Hg. Radiographs of the skull revealed a sella turcica approximately 15 per cent above the average normal in size and a calcified pineal gland. The basal metabolic rate was 19 per cent below the average normal. There was no impairment in sugar tolerance. The visual fields were normal.

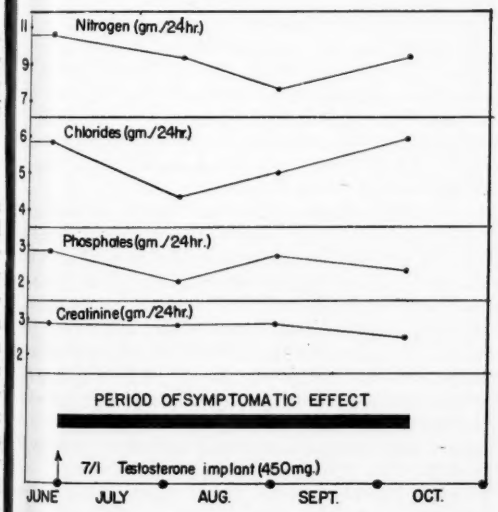
EXPERIMENT AND RESULTS

The diet, the manner of observation and the chemical procedures used were those described for *case 1.*



1. Effect of injection of testosterone propionate (250 mg.) and of an implant of testosterone (450 mg.) on the urinary excretion of nitrogen, chlorides and phosphates in a eunuchoid, 23 years old. 'Life of pellet' determined by excretion curve.

No preliminary injections of testosterone propionate were given. Following the implantation of 450 mg. of testosterone, studies were made at approximately monthly intervals for 3 months. Table 2 and figure 2 show the results obtained. The reduction in the urinary excretion of nitrogen, chlorides and phosphates was definite, though less marked than in the previous case. The clinical response was characteristic but also less pronounced than in *case* 1. With the onset of 'testosterone withdrawal' symptoms, the urinary findings showed a return to or near to the control levels. It may be of interest to record that during the entire period of observation, the patient was free of migraine headaches.



2. Effect of an implant of testosterone (450 mg.) on the urinary excretion of nitrogen, chlorides and phosphates in a eunuchoid, 28 years old. 'Life of pellet' determined by excretion curve.

CONCLUSIONS

1. The observation made by other workers that the injection of testosterone propionate is followed by a reduction in the urinary excretion of nitrogen, chlorides and phosphates, is confirmed.

2. Implanted pellets of testosterone initiate and maintain a reduction in the urinary excretion of these components during a period which coincides closely with that of the clinical response.

3. These observations suggest that the 'life' of a testosterone pellet may be demonstrated by the urinary excretion of nitrogen, chlorides and phosphates.

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Malignant Pheochromocytoma of the Adrenal Medulla (Paraganglioma)

Report of Case Simulating Carcinoma of the Adrenal Cortex with Secondary Adrenal Insufficiency

[Adrenal Medullary Tumor]

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It is customary to associate pheochromocytoma of the suprarenal gland with attacks of paroxysmal hypertension in which pallor, cold, clammy extremities, palpitation, 'pounding' of the pulse, particularly in the head and neck, and severe headache are constant findings, and in which a wide variety of other signs and symptoms of sympathomimetic type are common. Such attacks may be sufficiently severe to lead to death from cerebral hemorrhage, edema of the lungs, or coma symptomatically resembling that of uremia.

Despite the fact that only a few more than 100 cases of pheochromocytoma of the adrenal have been reported in the literature (1), the above syndrome associated with paraganglioma of a benign type is well understood, although not always recognized.

The clinical findings and course of malignant forms of the condition are not so well distinguished, as only 8 cases, including that herein described, are on record, not one of which has exhibited the acute attacks of widely fluctuating blood pressure and associated sympathetic phenomena above noted.

This difference in clinical course between the benign and malignant forms of the disease, as well as the rarity of the latter type, alone justifies further case studies. In addition, the Simmonds' or Addison-like syndrome observed in the case here reported, the unilateral position and large size of the primary lesion, and the location of a metastasis adjacent to the pituitary gland are features of unusual interest.

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CASE REPORT

K. F., D 959-40, a 43-year-old white woman, was admitted to the hospital because of weakness, loss of weight and pains in or about the rectum, the chest, the left leg, and the right hip and thigh regions. For 8 to 10 years she had not felt entirely well, had complained particularly of weakness, and had noticed a gradual darkening of her skin. Five months prior to admission, sharp, intermittent, knife-like pains were experienced in several locations, *a*), through the rectum, aggravated by defecation and associated with obstipation; *b*), through the chest, most marked on deep inspiration; and *c*), through the left leg, increased by weight bearing or walking.

There was an amenorrhea of 4 months duration. No history of hypertension or of attacks of paroxysmal hypertension could be elicited.

On admission, her status was that of an advanced malignant cachexia (fig. 1), in which the positive findings were extreme emaciation; the facies of pain; marked gingivitis and dental caries; darkening of the skin of the face, neck, and extremities with patchy areas of pigmentation over the trunk; a blood pressure of 114/80 mm. Hg; hard, bilaterally palpable submaxillary lymph nodes; tenderness over the lower ribs on both sides; some spasticity of the abdominal wall with a visible increased 'fullness' in the right upper quadrant; a palpable, non-tender mass, contiguous with and apparently continuous with the liver, the lower border of which was felt five fingers below the costal margin; a firm, non-tender spleen extending one finger's breadth below the left costal margin; tenderness to palpation and percussion over the right sciatic notch and the head of the left fibula; hyperactive superficial and deep-tendon reflexes; a Babinski reflex present on both sides; and a negative pelvic examination.

On laboratory examination, the urine was repeatedly negative. The blood always showed a secondary anemia, a typical count revealing a hemoglobin of 66 per cent; an erythrocyte count of 3.7 million per cu. mm.; a leucocyte count of 8,700 per cu. mm.; and a differential of polymorphonuclear neutrophiles 62, lymphocytes, 36, eosinophiles 1, and monocytes 1 per cent respectively. The speed of sedimentation of the erythrocytes (Westergren method) was 10 mm. in 15 minutes and 84 mm. in 1 hour. The icteric index was 4.9; the Takata-Ara reaction was weakly positive. The blood Wassermann reaction was negative.

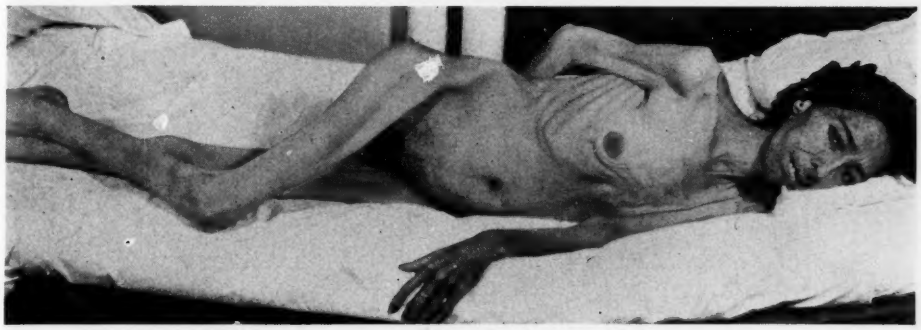

Fig. 1a

The basal metabolic rate was minus 22 per cent. The blood phosphatase was 3.9 Bodansky units per 100 cc. The total blood proteins were 5.8 gm. per cent, with albumin 3.4, globulin 2.4, and fibrinogen 0.33 per cent, respectively. Other blood chemical constituents in milligrams per cent were: total cholesterol, 148; esters, 102; dextrose, 84; non-protein nitrogen, 50; creatinine, 2.3; calcium, 9.3; inorganic phosphorus, 5.1; sodium, 292.3; potassium, 31.4. The electrocardiographic tracings were essentially normal.

Roentgenograms of the gastrointestinal tract revealed no abnormalities. Intravenous and retrograde pyelography showed a displacement downward of the right kidney with rotation of the upper pole forward and considerable angulation at the uretero-pelvic junction (fig. 2). Osteoclastic-metastatic lesions were demonstrated in the following bones: The second left rib and eleventh and twelfth ribs bilaterally; the antero-inferior spine of the left ilium; the supra-acetabular region of both sides; the upper third of the shaft, head, and neck of the right femur; the skull (fig. 3), particularly the frontal and parietal regions; the ninth dorsal and the first, third, and fourth lumbar vertebrae. Perirenal air insufflation failed to visualize satisfactorily the region of the right kidney or suprarenal.

Her course in the hospital was progressively downhill, to the time of death 5 months after admission, with evidence from time to time of further metastases in the skin, the brain, and various bones. Her blood pressure varied from 85 to 122 mm. Hg systolic, and from 70 to 82 mm. Hg diastolic throughout her last illness.

[1] Performed by Dr. Andrea Saccone, whose cooperation we hereby acknowledge with thanks.

At autopsy,[1] on opening the abdomen, 500 cc. of bloody peritoneal fluid were encountered. The liver extended about four fingers below the umbilicus. The aorta was negative except for a few atherosclerotic patches about the sinuses of Valsalva. The visceral and parietal pleurae overlying both lungs were studded with yellowish-grey sharply demarcated nodules, measuring from 1 to 20. mm. in diameter and eroding and partly destroying several sections of ribs bilaterally. There was a right lower broncho-pneumonia. The liver weighed 3,900 gm. Over its surface and throughout its parenchyma, there were innumerable yellowish-grey nodules varying in diameter from 1 to 13 cm. The spleen weighed 440 gm., but aside from congestion revealed no pathologic change. The left kidney and adrenal together weighed 100 gm., and showed no grossly abnormal alterations. There was a large, oval mass overlying the upper pole of the right kidney, which weighed 930 gm., and measured 15 cm. in its longest

Fig. 1b

diameter. On its surface and contiguous with it, the right adrenal cortex could be identified. The kidney was indented by the tumor but was not invaded by it nor attached to it. The mass was yellowish-pink in color, slightly irregular in shape, and circumscribed by a tense capsule. On cut section, a yellowish-green necrotic center was disclosed, surrounded by a pinkish cortex about 2.5 cm. thick.

A metastatic nodule was observed in the ninth thoracic vertebra. An intramural uterine fibroid 1 cm. in diameter was found.

The brain, weighing 1,190 gm., revealed no gross pathology on cut section. However, two-thirds of the right clinoid process appeared to be infiltrated with a soft, reddish, friable tissue. The dura and the skull both showed several greyish nodules scattered over the frontal and parietal regions, the largest of which measured 2 cm. in diameter.

Some histologic sections of tumor tissue taken from the primary growth (fig. 4a, 4b) and from its metastases in the liver, lungs, and pleurae, were treated with hematoxylin and eosin and others with Giemsa's stain. These revealed a rather uniform picture, with little variation of form or structure between the primary and the secondary lesions.

In the microscopic sections, the primary tumor lay in direct apposition to the cortex of the adrenal gland, being intimately attached to its fibrous tissue capsule. The growth was richly cellular and diffuse with a finely branching stroma throughout which there are numerous small blood vessels. A few minute foci of hemorrhage and necrosis are present. In a number of areas there is a tendency for the tumor cells to group themselves in a radiating or whorl-like manner about the blood vessels. The cells themselves are loosely arranged with indistinct boundaries and small granular fibres running between them. The cells vary markedly in size and shape, contain a small to moderate amount of cytoplasm, in which both eosinophilic and basophilic granules can be identified. With Giemsa's reagent (Schmorl technique), small, deeply staining, purplish granules can be seen within the cytoplasm of the cells and along the cytoplasmic processes between the cells. These are identical in character and disposition with granules observed in sections of normal adrenal medulla mounted and stained on the same slide with the tumor tissue.

The nuclei of the tumor cells are hyperchromatic. They vary as markedly in size as the cells themselves, and in shape, from nearly spherical through oval to markedly elongated structures.

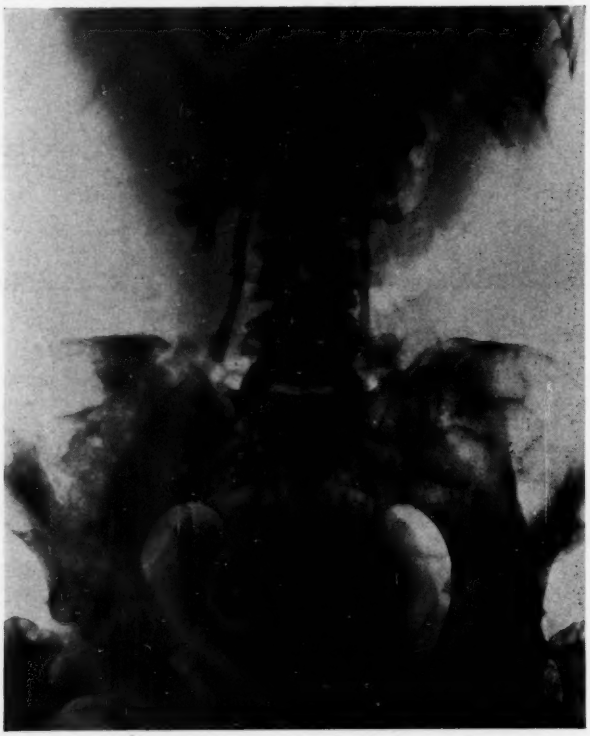

Fig. 2. Pyelogram. Note downward displacement, forward rotation and uretero-pelvic angulation of the right kidney.

Serial sections of the ovary, the pituitary, and the hypothalamus, and the infundibular stalk of the hypothalamus were made. Those of the ovary were stained with hematoxylin and eosin; those of the hypothalamus, with cresyl violet; alternate sections of the pituitary, with hematoxylin and eosin, and Mallory's stains, respectively; and alternate sections of the infundibular stalk, with Mallory's stain and Bodian's silver stain, respectively. None of these sections showed any pathological changes. In the anterior lobe of the hypophysis there was a slight increase in follicle-like cell groups surrounding small colloid filled lumina, a change not uncommonly seen in the normal gland. Multiple sections of the thyroid, the left adrenal, and the pancreas stained with hematoxylin and eosin revealed no pathological changes. The small colloid cysts seen in the thyroid could not be looked upon as abnormal, as they are frequently seen in the apparently normal gland.

The pathological diagnoses included bronchopneumonia; myoma of the uterus; hyperplastic splenitis; hemoperitoneum; malignant pheochromocytoma of the right adrenal medulla with widespread metastatic foci in the skull, vertebrae, ilia, hips, tibiae, fibulae, ribs, lungs, pleurae, liver, and skin.

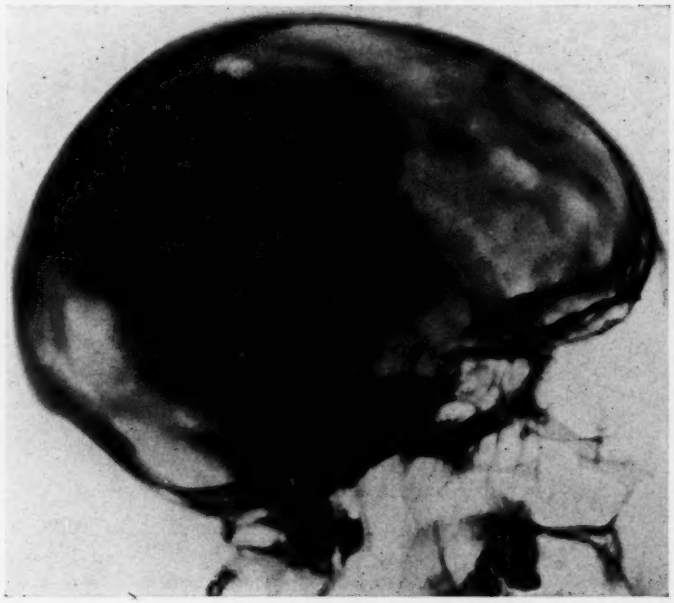

Fig. 3. Roentgenogram of the skull, showing osteoclastic metastases.

DISCUSSION

Up to 1932, 1 questionable and 5 proved cases of malignant pheochromocytomata of the adrenal medulla had been recorded (2). Since that time, we have found reports of 3 cases which were undoubtedly malignant (3, 4), and 4 which were histologically but not clinically so (3, 5, 6, 7). In one of Lewis and Geschickter's cases (3), metastases were seen in the kidney and the neighboring lymph nodes; in the other, only in the neighboring lymph nodes. McKenna and Hines (4) could find no metastases in their patient at the time of operation. However, Biskind and his associates (8), in a tabular summary of all operated cases state that McKenna and Hines' patient died 2 years following operation as a result of metastases, the location of which was not mentioned. In the remaining 6 cases in which metastases have been reported, they were as widespread as in the patient herein described.

Inasmuch as histologic features usually denoting malignancy are a rather characteristic and diagnostic feature of the most benign of pheochromocytomata of the adrenal medulla, it seems likely that all of the cases in which metastases did not occur should be classified as benign.

In the present instance, had it not been for the large mass in the upper right quadrant of the abdomen extending well down towards the iliac crest laterally, an antemortem diagnosis of Simmonds' cachexia would have been seriously considered. In view of the mass, the pigmentation, the electrolytic and other metabolic disturbances, it was believed that we were dealing with a carcinoma of the adrenal cortex with a secondary adrenal insufficiency, a syndrome which has been observed in several patients (9–12). An attempt was made to confirm this impression by an

estimation of the estrogenic hormone in the urine, for which in a single study a high value was obtained. However, too few animals were used in the determination to warrant a satisfactory deduction and unfortunately, opportunity to repeat the bioassay with a larger number did not present itself.

The true nature of the tumor was not suspected during life, as its large size, its confinement to one adrenal, and the accompanying Addisonian syndrome are unusual features of malignant paraganglioma.

their patient, but many other features of Addison's disease were lacking. The patient had a pulmonary tuberculosis to which death was attributed.

The present patient exhibited all of the features of Addison's disease, including the excessive loss of salt from the body and a retention of potassium. As in the case of Riemer's patient, no gross or microscopic alteration of cortical tissue could be observed. Moreover, serial sections of the pituitary gland revealed no abnormalities. The observed disturbances,

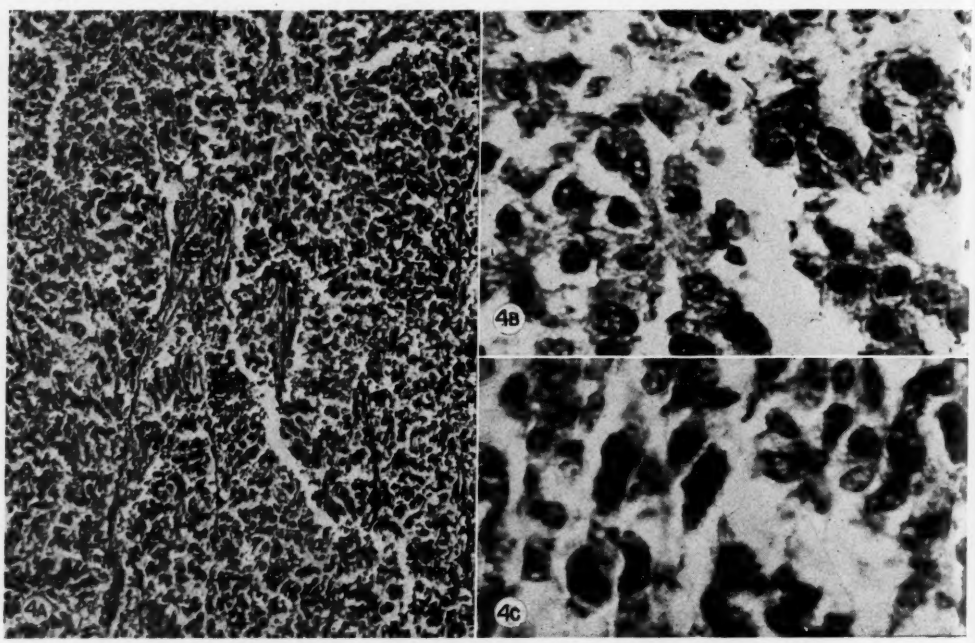

Fig. 4a. Section of tumor (×170). Note the tendency to a lobulated growth in which groups of large cells are separated by a fine, fibrovascular stroma. (H & E stain).

Fig. 4b. Section of tumor (×930). Note the marked variations in nuclear size and staining. Mitotic figures can be seen near the center of the field. (H & E stain).

Fig. 4c. Section of tumor (×930). This section was treated with Giemsa's stain (Schmorl technique). The dark granules in the cytoplasm of the tumor cells reacted to this stain in a fashion similar to that seen in the cytoplasm of the medullary cells of the normal adrenal gland simultaneously mounted and stained with them.

Syndrome of Addison's Disease in Pheochromocytoma of the Adrenal

Two reported cases of benign pheochromocytoma of the adrenal were associated with features suggestive of Addison's disease (13, 14). In Riemer's patient (13) there was a cystic tumor of the right suprarenal medulla. The cortex was intact, and neither grossly nor microscopically could any disturbance of the right or left adrenal cortex be made out. There seems to be little doubt, however, that the patient died in adrenal insufficiency. Laignel-Lavastine and Aubertin (14) mentioned a widespread melanoderma in usually looked upon as pathognomonic of insufficiency of the cortex of the adrenal, are in the present state of our knowledge unexplainable. This is the first patient with a malignant type of pheochromocytoma to present them.

Disturbances of Adrenal Cortex Other Than Addison's Disease, Associated with Paraganglioma of the Medulla

In one instance, a chromaffinoma appears to have produced androgenic effects without any morphologic alteration's being detected in the adrenal cortex

(15). Neff's patient, a girl of 16 months, in addition to the paroxysmal hypertension, developed hirsutism, acne, and hypertrophy of the labia and clitoris, all of which receded a few weeks after the removal of a 96-gram tumor. There was no gross or microscopic evidence of involvement of the adrenal cortex. These several cases in which paraganglioma has been associated with functional alterations in the adrenal cortex imply a closer relation than hitherto realized in the integration of the functions of these two portions of the gland.

Alterations in Other Endocrine Glands Associated with Pheochromocytoma of the Adrenal

Other glandular disturbances seen in association with paragangliomata of the adrenal medulla have included a colloid adenoma of the thyroid gland (16); a papillary adenoma-carcinoma of the thyroid without metastases (2); and diabetes mellitus (none reported since the 5 cases cited by Eisenberg and Wallerstein (2); symptoms of hyperthyroidism and hypertrichosis in a single patient, in whom, however, a diseased thyroid was not present (17); and a girl with hypertrichosis and deficient mammary development without disease in other endocrine organs (18).

Clinical Features of Malignant Pheochromo cytomata of the Adrenal Medulla

From an analysis of the 8 known cases of malignant paraganglioma of the adrenal medulla, the following features warrant comment.

a). *Sex.* Three of the patients were males; 3 were females; and in the report of 2 cases the sex was not given.

b). *Age.* In the 6 instances in which ages were mentioned, they were 30, 34, 43, 47, 51, and 68 years, respectively, with an average age at the time of first observation of 45.5 years.

c). *Size and location of tumor.* In but 3 of the 8 cases is the size of the tumor mentioned. One of these was 5 cm. in diameter; the second, '5×2 cm.'; and the third, the case herein described, a nearly spherical mass 15 cm. in its greatest diameter. It is interesting to note that while gangliomata of histologically benign type have been known to reach a size of 12.5 cm. in diameter (19), no malignant paraganglioma of more than 5 cm. in diameter has been previously described.

The paraganglioma was bilaterally situated in 5 of the 8 patients; it was confined to the right side in 1, and to the left side in 2.

d). *Symptoms and signs.* Symptoms suggestive of a malignant growth were noted as much as a year prior to coming under observation (20). In one instance, weakness and increasing pigmentation of the skin were of from 8 to 10 years' standing (present case). All of the patients, sooner or later, developed marked loss of weight with cachexia. Pain was universally present in every case and was referable either to the primary tumor or to its metastases. Epigastric distress due to encroachment of the primary tumor was mentioned in Cohn's case (quoted by Geschickter 5), and was noted in our own. Pains were reported in the region of metastases in all of the cases in which clinical history was available.

In Geschickter's patient (5), constipation and night sweats were prominent symptoms. One patient had a persistent cough and coarse râles over the bases and left upper lobe of the lungs consequent upon metastases to that organ.

Blood pressure is mentioned in 3 patients. In none of them was there hypertension; and in King's (20) and our patient actual hypotension existed. In no instance was there any intimation that bouts of paroxysmal hypertension existed or had existed at any period of the patient's life. Inasmuch as such attacks are looked upon as pathognomonic of paraganglioma, it seems important to emphasize not only their complete absence in the malignant forms, but also their failure to occur in slightly less than 50 per cent of the benign cases (2).

A palpable mass was found on the right side in two patients (present case and 2), and on the left in one (5).

Widespread metastases were visible and palpable in the skin in two instances (20 and present case).

e). *Metastases.* The regional lymph nodes were involved in all patients, and were the only point of metastasis noted in one (Cohn's case cited by Geschickter 5). Lymph nodes of the thoracic cavity were invaded in 5 instances, and involvement of the lymph nodes in the region of other metastases has been variously recorded. The liver was enlarged and the seat of secondary growth in at least 4 of the 8 patients (2, 20, 21, present case). Widespread metastases to bony structures have been observed (2, 20). The vertebrae, the ribs, the pelvis, the cranium, and the femora have been involved with a frequency somewhat in the order named. Three patients exhibited widespread metastases to the lung (2, 20, present case). The pleurae (22, present case) and the skin (20, present case) were the seat of secondary malignancy in two instances each. Among other locations of metastatic invasion, the intestines (2) and the kidney (5) have been mentioned.

SUMMARY

1. The eighth reported case of malignant paraganglioma of the adrenal medulla with widespread metastases is described.

2. The absence of bouts of paroxysmal hypertension in patients with the malignant form of paraganglioma is emphasized.

3. The right adrenal medulla was the only endocrine structure to show gross or microscopic changes of a pathologic nature.

4. Unusual features observed in the present instance of paraganglioma of the adrenal medulla included an Addisonian-like syndrome in the presence of histologically normal pituitary and adrenal cortical tissues; the strictly unilateral adrenal involvement; and the large size of the primary tumor.

5. The major features of malignant pheochromocytomata of the adrenal are summarized.

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Potassium Tolerance Test as an Aid in Diagnosis of Adrenal Insufficiency

[Adrenal Insufficiency]

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THE TYPICAL SIGNS AND SYMPTOMS of Addison's disease rarely become manifest until extensive damage has been done to the adrenal cortex. It is not the well-defined adrenal cortical failure that tests the diagnostic acumen of the physician, but the borderline case. A procedure to discern early hypoadrenia would be of inestimable value. At present there are a few procedures which have been advocated as an aid for the early diagnosis of hypoadrenia. Wilder (1) described a diagnostic test for the determination of adrenal cortical failure which is based on the concentration of the urinary chloride after the intake of sodium, potassium and water has been controlled for a period of 3 days. However, its value in early cases of hypoadrenia is questionable, since it must be done in a hospital and it frequently makes a patient who has Addison's disease severely ill. The findings furthermore are often indecisive in the indefinite case. Robinson, Power and Kepler (2) described two new procedures to aid in the recognition of Addison's disease. These tests are based on the facts that *a*), in most cases of Addison's disease, the kidneys continue to secrete fairly concentrated urine even after water has been ingested; *b*), patients suffering from Addison's disease tend to excrete excessive amounts of sodium chloride but retain urea. The authors explain that these procedures are particularly useful in eliminating insufficiency of the adrenal cortex as the cause of fatigue states. They do not advocate these procedures as a means of proving the function of the adrenal cortex to be normal. Thorne (3) suggests that a good diagnostic method is the therapeutic test.

This paper will devote itself to a discussion of the potassium tolerance test, which was devised by Zwemer (4) in 1936 to determine mild adrenal cortical insufficiency.

The adrenal cortex is affected in numerous diseases and conditions (5). Severe burns, food poisoning and a variety of acute infections, according to Aschoff, Goldzieher and Dietrich, will cause hyperemia, edema and focal necrosis in the adrenal cortex. Diphtheria and scarletina cause marked injury to the cortex but not to the medulla. Following severe trauma and secondary shock the adrenal cortex becomes rapidly depleted of lipoid, and cellular necrosis appears. In all of these injuries and diseases the plasma potassium is high.

Zwemer and Truszkowski believe that the symptoms of adrenal cortical insufficiency are in many respects identical with potassium poisoning and that a disordered potassium metabolism is the primary defect of adrenal cortical insufficiency. It is possible to postulate that the adrenal cortex is affected by many more conditions than is at present known, so that a positive potassium tolerance curve may be obtained in diverse conditions.

In experimental adrenal insufficiency in animals there is an increased susceptibility to exogenous potassium (6). The plasma potassium of normal animals is not affected by the ingestion of potassium. In adrenal insufficiency in human beings there is a rapid and very considerable rise in the plasma potassium after the ingestion of 10 mg. of potassium per pound of body weight (7). The test is performed as follows. From a fasting patient, capillary or arterial blood is taken and a potassium drink having the equivalent of 10 mg. of potassium per pound body weight is given. Blood is then taken at the end of 30, 60 and 120 minutes and the potassium of the plasma is determined. The resultant curve in a normal individual will be flat or show no more than a 10 per cent rise. Zwemer (8) found the greatest value of this test in cases of asthenia and hypotension. Patients with these symptoms having a positive potassium tolerance curve, treated with adrenal cortical extract, had a complete alleviation of their symptoms. Patients with a normal potassium tolerance curve, with the same symptomatology, had no relief with adrenal cortical extract.

Recently, Green, Levine and Johnston (9) reported

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the value of determining the potassium tolerance curve. They came to the conclusion that the test was not diagnostic since they found abnormal curves in cases of bromism, neurasthenia and nephritis, while in two cases of Addison's disease the curve was normal. They mention, however, that their technique was different from Zwemer's. Zwemer specifically states that the blood must be arterial, since the potassium content of venous blood varies because potassium is an intracellular substance and so will vary in the venous blood.

We have performed 43 tests following Zwemer's technique on 42 patients (as shown in the accompanying table), and have obtained 12 abnormal curves.

TABLE 1. POTASSIUM TOLERANCE IN VARIOUS TYPES OF PATIENTS

Diagnosis	Number of Cases	Potassium Tolerance Curve	
		Normal	Abnormal
Hirsutism	16	15	1
Allergy	6	5	1
Menopause	3	3	
Pituitary adenoma	3	1	2
Basophilism	2		2
Addison's disease	2		2
Nephritis	2	2	
Asthenia	2		2
Obesity	1	1	
Hypertension	1	1	
Male climacteric	1		1
Metrorrhagia	1	1	
Adrenal cortical carcinoma	1	1	1

CASE REPORTS

Case 1, L.F. A 44-year-old white male was admitted to the hospital on 4/20/40 with symptoms of weakness and dizziness of 7 months duration. In 1938 he had been treated for bilateral pulmonary tuberculosis with a right phrenic crush. On admission physical examination revealed a thin brownish-looking male complaining of weakness, tiredness and dizziness. There was brown pigmentation over the entire body. Blood pressure was 88/65 mm. Hg. The electrocardiogram and intravenous pyelogram were normal. The basal metabolic rate was −2, the blood urea 9.8, uric acid 6.3, cholesterol 366 mg. %, and the sodium was 314 mg.; this latter dropped to 297. A roentgenogram of the lungs showed the presence of a productive type of apical tuberculosis without cavitation. The diagnosis was Addison's disease and he was given a high salt and low potassium diet with striking subjective improvement.

Case 2, C.S. A 40-year-old white female was admitted to the hospital on 1/27/40 with complaints of progressive weakness and skin pigmentation for the past two years. She had marked emotional lability. Physical examination revealed no gross pathology. The blood pressure was 98/68 mgm. Hg and the sodium was 292 and 295 mg. on two different occasions. No treatment was given.

Potassium Tolerance, mg. %

Case 1		Case 2	
Fasting	21.3	Fasting	18.2
½ hr.	26.5	½ hr.	21.0
1 hr.	30.3	1 hr.	22.2
2 hr.	32.4	2 hr.	22.2

These two cases of Addison's disease showed positive potassium tolerance curves as was expected.

Case 3, R.J. A 36-year-old white female entered the Endocrine Clinic with complaints of weakness, tiredness and dizziness. Physical examination revealed no gross abnormalities. The blood pressure was 100/60 mm. Hg and there were a few pigmented spots on the buccal mucosa and face. She was put on a high salt diet with remarkable relief of her complaints. The blood pressure rose to 120/74 mm. Hg. Cessation of salt administration was followed by recurrence.

Case 4, M.G., a white adult female entered the Endocrine Clinic with complaints of amenorrhea, backache, headache, tiredness and drowsiness. Physical examination revealed a small adenoma of the thyroid and some yellowish areas of pigmentation on the face. Blood pressure was 114/70 mm. Hg, and sodium 306 mg. She was put on a high salt diet with excellent improvement in her general well-being.

Potassium Tolerance, mg. %

Case 3		Case 4	
Fasting	16.3	Fasting	22.0
½ hr.	22.0	½ hr.	22.9
1 hr.	22.2	1 hr.	23.5
2 hr.	22.2	2 hr.	25.0

These are two cases of asthenia that are probably early cases of hypoadrenia. They both felt very much better when put on a high salt diet.

Case 5, G.F., a 53-year-old white female was admitted to the Endocrine Clinic because of acromegalic facies. Her appearance had changed completely in the past 3 years. At present she was complaining of headaches, weakness and tiredness. Physical examination revealed an obese woman without demonstrable pathology. Roentgenograms of the sella turcica showed a broadened sella with loss of density in the bony markings of the floor; the posterior clinoid processes were thin. A hyperostosis frontalis was present. The basal metabolic rate was +4, cholesterol 305, calcium 11, phosphorus 3.8 mg. %. The blood sugar leads in a glucose tolerance test were 83, 162, 120, 108 mg. % after 0, ½, 1 and 1½ hours respectively. The visual fields showed concentric narrowing. She received roentgen-ray therapy to the pituitary with improvement n her headaches though she still complained of tiredness and weakness.

Case 6, L.W., a 49-year-old white female entered the Endocrine Clinic complaining of headaches, dizziness and attacks of weakness. In 1935 roentgenograms showed enlargement of the sella turcica with erosion of the dorsum sellae. She received at that time 4,240 r of roentgen therapy. In April, 1939, the skull showed no change. In March, 1940 she entered the Endocrine Clinic with the above complaints. Roentgenograms showed further enlargement of the sella. 2,560 r roentgen therapy was given.

The visual fields were normal. There was slight hirsutism of the arms which was first noticed 7 years ago. Blood pressure was 150/110 mm. Hg. The B.M.R. was +13 and sodium 324 mg. %.

Potassium Tolerance, mg. %

Case 5		Case 6	
Fasting	17.1	Fasting	17.4
½ hr.	18.2	½ hr.	16.6
1 hr.	20.4	1 hr.	19.4
2 hr.	19.5	2 hr.	19.5

These two cases of pituitary adenoma were probably in a period of relative pituitary failure so that we can postulate a depression in the production of the adrenotropic factor causing a secondary adrenal cortical insufficiency.

Case 7, M.M. A 46-year-old white male entered the Endocrine Clinic on Oct. 10, 1940, with the complaint of generalized weakness. Past history was negative except for attacks of gonorrhea in 1919 and 1923. In April of 1940 he had an attack of angina pectoris which was not severe and he continued to work. However, because of weakness he stopped working. He was in the Veterans' Hospital for 4 weeks. On admission he complained of generalized weakness, impotency and loss of libido. His appetite was good and he had gained 20 pounds in the past year. Physical examination revealed a well-developed plethoric male. His heart was enlarged to the left and right with no murmurs. His weight was 222 pounds, height 68½ inches, span 68¼ inches, lower measurement 35, and the blood pressure was 190/120 mm. Hg. Cardiogram showed myocardial involvement. The B.M.R. was +1, the blood sugar levels in a glucose tolerance test were 121, 193, 266, 157 mg. % at 0, ½, 1 and 1½ hours, respectively with a spilling of sugar after 1 and 2 hours. Calcium was 9.9 and phosphorus, 3.5 mg. %. Test of the urine for prolan and estrin were negative. Roentgenograms of the skull showed a densely calcified pineal. He did not return for treatment.

Case 8, S.P. A 25-year-old white female entered the Endocrine Clinic on 11/22/40 with a chief complaint of obesity which had failed to decrease with diet. Seven months ago the menses became delayed, occipital headaches started and hair on the face started to grow. Physical examination revealed an obese female with striae over the abdomen and near the axillae. Heart and lung findings were negative. Fingers were short. Blood pressure was 160/120 mm. Hg. Weight was 284 pounds, height 66 inches, span 68 inches, and lower measurement was 33½ inches. The eye grounds and visual fields were normal. Roentgenograms of the sella and intravenous pyelogram were normal. Urine analyses showed that prolan was present and estrin to the amount of 4 R.U. B.M.R. was +7, cholesterol 368 mg. %, sodium 322 mg. and blood sugar values in a glucose tolerance test were 94, 131, 158, 124 mg. % at 0, ½, 1 and 1½ hours, respectively. She was given estradiol benzoate, 2,000 R.U. twice weekly.

Potassium Tolerance, mg. %

Case 7		Case 8	
Fasting	19.8	Fasting	20.0
½ hr.		½ hr.	22.9
1 hr.	24.2	1 hr.	22.9
2 hr.	20.0	2 hr.	24.2

In these two cases of basophilism there is no evidence of any adrenal cortical insufficiency.

Case 9, M.H. A 44-year-old white male diabetic entered the Endocrine Clinic on 10/21/40 because of impotency of 8 months duration, weakness and tiredness. Physical examination revealed a slender hirsute individual with well-developed genitalia and brown pigmented areas on the face. Blood pressure was 135/40 mm. Hg; height, 67 inches; weight, 143 pounds; span, 67 inches, the B.M.R., +4. Skull roentgenograms were normal. He received thyroid medication without improvement, then placebos and salt. He stated that he felt considerably better. He was then given methyl testosterone, 30 mg. daily with no improvement.

Case 9, K Tolerance mg. %

Fasting	20.0
½ hr.	23.2
1 hr.	23.5
2 hr.	23.0

Here again there is no definite evidence of any adrenal cortical insufficiency although the good response to salt therapy is indicative of adrenal cortical involvement.

Case 10, B.K. A 26-year-old white female was admitted to the hospital on 10/2/40 with complaints of hirsutism, amenorrhea and pain in the right costovertebral region for 3 years. On Dec. 21, 1938, she had been operated on and an adrenal carcinoma had been removed. On admission an intravenous pyelogram showed an extrinsic deformity at the superior angle of the right kidney. Roentgenograms of the lungs showed metastatic infiltration. On October 14 the blood pressure was 170/112 mm. Hg. On October 20 the patient suddenly went into collapse simulating an Addisonian crisis. The blood pressure at this time was 72/50 mm. Hg. The patient died Nov. 1, 1940.

Case 10, K Tolerance, mg. %

	A.	B.
Fasting	20.0	19.0
½ hr.	19.2	19.9
1 hr.	20.0	22.2

Here we find a patient with an adrenal cortical carcinoma had a normal potassium tolerance curve, but as soon as an adrenal failure set in, the tolerance curve became abnormal.

Case 11, M.Z. A 12-year-old white boy suffering from asthma and allergic rhinitis who had been treated unsuccessfully in the Allergy Clinic entered the Endocrine Clinic. The B.M.R. was −18 and he was given thyroid, 0.5 grain daily and felt better for a time but attacks of asthma started again. He was then given desoxycorticosterone[1] with improvement. Treatment was voluntarily stopped and asthmatic attacks recurred. No improvement was noted when treatment was repeated.

Case 11, K Tolerance, mg. %

Fasting	18.2
½ hr.	19.3
1 hr.	20.5
2 hr.	22.9

There is no direct evidence that the adrenal cortex is involved in the allergic states. However, when histamine or anaphylactic shock is induced in animals the adrenal cortex shows necrosis and loss of lipoid in the cells. The tissues of adrenalectomized animals are also high in histamine content. So if we assume, as has been suggested, that the allergic state is due to a liberation of histamine, it is possible that a diminished cortical activity is present.

Case 12, F.K. A 21-year-old white girl entered the Endocrine Clinic on 9/21/40 with the complaints of hirsutism and weakness. Menses began at 11½ years, were irregular and lasted 4 to 5 days. Physical examination revealed a tall, thin, angular female with facial hirsutism and acne. Blood pressure was 120/68 mm. Hg, height 68½ in., weight 120 lb., span 66 in., and lower measurement 37½ in. The clitoris was slightly enlarged and there was a male escutcheon. The uterus was small. Epiphyseal union was normal. The B.M.R. was −10, cholesterol 229 mg. %, prolan negative, estrin 2 R.U. Blood sugar values in a glucose tolerance test were 81, 168, 108, and 73 mg. % after 0, ½, 1 and 1½ hours, respectively. Intravenous pyelogram was normal. She was given desoxycorticosterone with no improvement.

Case 12, K Tolerance, mg. %	
Fasting	16.6
½ hr.	22.2
1 hr.	18.2
2 hr.	16.6

In this case, as has been suggested, we can assume an overactivity of the androgenic function of the adrenal. The gland presumably functions pathologically and an excess of androgenic substance is liberated causing secondary masculine changes or there is a conversion of the normal hormone to an abnormal one which assumes masculinizing activity at the expense of the salt-regulating activity.

CONCLUSIONS

We have noted that the potassium tolerance test gives a specific response in Addison's disease and in other conditions in which there is a possible adrenal cortical insufficiency. At present we do not believe this test to be too specific and it might be simpler to use salt as a therapeutic test. The only advantage of the potassium tolerance test is in its objectivity.

We hope in the near future to report on a large series of cases of asthenia, since we believe that this test is of definite value in this type of ailment.

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[1] The desoxycorticosterone used was supplied by the Schering Corporation, Bloomfield, N. J.

Clinical Report of the Treatment of A Case of Pemphigus with Desoxycorticosterone Acetate

[Adrenals and Pemphigus]

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ANY DEFINITION of pemphigus has heretofore included in its formulation three principal characteristics. It has been described as an acute or chronic inflammatory disease of the skin, of unknown etiology, that often terminates fatally. In the light of recent investigation, this formulation requires revision. Although the full etiology of pemphigus remains undetermined, important contributory factors in the form of adrenal involvement have been demonstrated. Secondly, while the cutaneous manifestations still remain outstanding, fundamental alterations in salt and water metabolism have been demonstrated. Lastly, treatment aimed at the metabolic disturbances has produced remissions and cures of the manifestations of pemphigus.

Talbott (1, 2) and his co-workers investigated intensively a group of 24 cases of pemphigus from the metabolic point of view. Of these 24 cases, 10 were acute pemphigus and manifested the most outstanding and consistent changes in salt and water metabolism. These changes were: *a*), An invariable lowering of the serum sodium chloride, the deviation from the normal being associated with the mass of skin involved and the severity of the clinical condition. *b*), Lowering of the serum protein with reversal of the albumin-globulin ratio. *c*), Increase in the plasma volume and total interstitial fluid. The results of kidney function studies were negative, indicating that these metabolic disturbances occurred in the absence of tubular or glomerular damage.

Since all of the serum changes observed, except for the serum protein variations, can be found in adrenal insufficiency, treatment was aimed at rectifying this deficiency. The 10 cases of acute pemphigus were divided into two groups of 5 each. The control group received at one time or another, almost every form of therapy, ranging from whole blood transfusions to parenteral liver, sulfanilamide, yeast and cod liver oil; from salyrgan and ammonium chloride to Fowler's solution, ascorbic acid and thiamin chloride. All 5 of these patients died.

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The other 5 cases were treated with adrenal cortex extract and sodium chloride. In this group, two cases developed remissions which have lasted in one for 3.5 years and in the other for 3 years. In the other three cases, remissions were also induced. However, relapses followed cessation of therapy, and resumption of therapy after one or more relapses eventually was ineffective.

Finally, postmortem examination of 3 of the patients with acute pemphigus revealed, in 2 of the 3, gross adrenal damage.

Whatever the underlying causes may be, there can be little doubt that the alterations in salt and water metabolism in this disease, play a fundamental rôle. Any treatment aimed at returning these fluid and salt changes to normal, if successful, should play an important part in ultimate complete recovery.

In the following clinical case report[1] we wish to describe a case of acute pemphigus treated with these principles in mind.

CASE REPORT

G. B., a 61-year-old male, an operator at dresses, was admitted to the Bronx Hospital Dec. 9, 1940 with complaints of itching and a rash of 2 weeks' duration. His family history and past history were essentially negative. His present illness began two weeks prior to admission with itching and rash of the upper back. As a result of itching and constant scratching, the rash spread, soon involving the entire body. The patient gave no history of taking any medication except allophen, which laxative he had been taking nightly for the previous 2 to 3 years.

On admission, the patient was found acutely ill, in anguish as a result of itching and furious scratching. The positive physical findings were: *a*), a coarse tremor of the right hand and forearm of one year's duration; *b*), erythmatous, eczematoid skin eruption with patches all over the body except for the head. There were numerous bullae on the inflammatory areas. The bullae were tense and contained clear fluid. There were no oral lesions. The temperature was 101° F, hemoglobin 94 per cent, red blood cells 4,800,000, white blood cells 11,600 with 85 per cent

[1] We are grateful to Dr. Samuel Feldman for permission to investigate and treat this patient.

polymorphonuclear leucocytes. Blood Wassermann reaction was negative. The values for blood sugar, blood urea and blood creatinine were essentially normal.

The first differential diagnosis lay between a bullous erythema multiforme, possibly on the basis of the drug allophen, and pemphigus.

The patient was immediately started on potassium permanganate baths, colonic irrigations, low protein diet, salol and icthyol and calamine lotion. The itching continued and many new bullae appeared on the body. Ten days after admission the inflammatory condition of the skin had partially subsided and many new bullae were appearing on a non-inflammatory base. The diagnosis of pemphigus appeared definitely justifiable at this time. The patient was, therefore, given 1 gram of sulfathiazole every 6 hours. Six days later, because the sulfathiazole concentration was only 2 mg. per cent and there had been no change in the patient's condition, the dosage was increased to 1 gram every 4 hours. The temperature continued to fluctuate between 99 and 101° F. Ten days after starting the sulfathiazole therapy, the patient's condition appeared worse, and there were many new bullae.

Sulfathiazole was, therefore, discontinued and the patient was given intravenous .9 per cent calcium gluconate and sodium arsenate solution. His condition remained unchanged, however. Therefore, after 2 weeks of therapy the arsenate and calcium gluconate were discontinued and only Balsam of Peru and zinc oxide were used locally on the body and legs.

Examination of the fluid of the bullae at this time showed a sodium chloride content of 528 mg. per cent. Because of the apparent disturbance of the fluid and salt metabolism, the patient was given at this point, 9 weeks after the onset of his illness, desoxycorticosterone acetate.[2] Five mg. of desoxycorticosterone acetate were given 3 times daily for 3 weeks and then the drug was reduced to 5 mg. daily. Within a week after starting this therapy the patient began to show a slow but steady improvement and at the time when the dosage was decreased there was marked improvement, all scratching and itching having ceased and only occasional rare new bullae appearing. After 5 weeks of treatment, no new bullae appeared at all. During this period of desoxycorticosterone acetate therapy, the blood pressure was maintained between 100/60 and 110/70 mm. Hg. Several furuncles and carbuncles had appeared earlier and these were treated with shortwave diathermy. Seven weeks after beginning the desoxycorticosterone acetate therapy, the patient was discharged in good condition.

He was seen in the Endocrine Clinic 6 weeks later, at which time his condition was good, no new bullae having appeared. His blood pressure was 160/85 mm. Hg. Five weeks later, a total of 11 weeks following cessation of therapy, occasional small blebs began to appear on his arms. He was, therefore, given 5 mg. of desoxycorticosterone acetate 3 times weekly and within 2 weeks there were no more blebs. Treatment was continued for another 2 weeks and was then discontinued.

[2] The desoxycorticosterone acetate (Cortate) was supplied through the courtesy of Dr. Max Gilbert of the Schering Corporation, Bloomfield, N. I.

Ten days later blisters began to appear once more on the upper and lower extremities. The patient was observed without therapy for 10 weeks. During this period 2 to 3 fresh blebs continued to appear daily. Systolic pressure was maintained between 155 and 160 mm. Hg.

At the end of this period of observation the patient was given once again desoxycorticosterone acetate, receiving 5 mg. twice weekly. After the first 10 days no more blebs appeared. A total of six injections were given and the desoxycorticosterone acetate was then discontinued. In the period of 5 months since the final cessation of treatment, there have been no new blebs. Blood pressure is 170/100 mm. Hg. Examination of the skin of the abdomen shows numerous small brown pigment spots at the site of the former blebs.

DISCUSSION AND CONCLUSION

The impressive response of this patient to adrenal hormone therapy is additional support of the work of Talbott (1). One important difference should be noted. Talbott observed that relapses proved progressively resistant to therapy until death intervened. In our case relapses were mild and were controllable within 10 days by the resumption of adrenal cortex hormone in small doses. Whether this depends on the use of desoxycorticosterone acetate instead of the adrenal cortex extract, needs further investigation.

It is apparent that the development and maintenance of a state of altered permeability and deranged salt and water metabolism plays an important rôle in the clinical course of pemphigus. Winter and Hartman (3) have demonstrated a water shift in the muscles of the adrenalectomized animal. Talbott (1) et al. (2) have found alterations in salt and water metabolism in 10 cases of acute pemphigus, similar to the alterations observed in adrenal insufficiency. With these findings in mind, it would appear consistent and logical to undertake the treatment of the manifestations of pemphigus as the manifestations of an adrenal insufficiency. It would appear to be desirable to use the extract of the whole adrenal cortex for this purpose. However, in our case, desoxycorticosterone acetate was used because therapy was aimed directly at the alteration in salt and water metabolism and, therefore, the most potent available fraction for the purpose was used.

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COMMUNICATIONS TO THE EDITORS

Inhibition of Lactation
II. Oral Use of Methyl Testosterone

In a previous communication[1] we reported on the percutaneous use of the male sex hormone, for the inhibition of lactation. We found that it was effective in 68 per cent of our cases resulting in *a*), a diminution in the degree of lactation; *b*), in the lack of breast engorgement and *c*), in the absence of pain. The method of administration, however, was bothersome to the nursing staff. With the advent of methyl testosterone we wished to determine whether equally good results could not be obtained by its oral administration.

Twenty-five cases from the obstetric service of the Bronx Hospital were therefore treated with tablets of the male sex hormone. Each tablet contained 10 mg. of methyl testosterone and was administered beginning 40 hours after delivery according to the method of Duffy and Corsaro.[2] The patients were given three 10-mg. tablets 3 times a day for 3 days; a total of 270 mg. of methyl testosterone.* Of importance was this fact, that methyl testosterone was given at the beginning of lactation, that is, on the second day after delivery.

There was complete inhibition of lactation in 23 of the 25 cases (91%). Two patients did not respond to the above amount and showed no response to additional therapy. Tight breast binders, catharsis and rigid limitation of fluids were purposely omitted and were found not to be required.

SUMMARY

Methyl testosterone, orally, can be substituted for testosterone propionate, parenterally or percutaneously, for the inhibition of lactation in the post-partum patient.

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Received for publication March 16, 1942.

[1] Fleischer, A. J., and J. I. Kushner: *J. Clinical Endocrinology* 1: 407. 1941.

[2] Duffy, P. V., and J. Corsaro: *J. Am. Med. Assoc.* 116: 33. 1941.

* The methyl testosterone (Neo-Hombreol M) used in all cases in this paper was supplied through the kindness of Dr. M. C. James of Roche-Organon, Inc., Nutley, New Jersey.

Abstracts of
CURRENT CLINICAL LITERATURE

Editor: DANIEL A. MCGINTY. *Collaborators:* E. B. ASTWOOD, ISRAEL BRAM, JOHN C. BURCH, JOHN C. DONALDSON, MURRAY B. GORDON, E. C. HAMBLEN, FRANK A. HARTMAN, R. G. HOSKINS, J. E. HOWARD, ALLAN T. KENYON, J. T. LEWIS, JOSEPH M. LOONEY, A. E. MEYER, C. A. PFEIFFER, EMMERICH VON HAAM.

ENDOCRINE GENERAL

ANONYMOUS.

Antihormones. *Lancet* 242: 203. 1942.

This review points out that if animals are given repeated injections of certain hormones, especially A P extracts, they become insensitive to the physiological action of the hormones. Collip and Anderson (1934) demonstrated that the refractory state depends upon inhibitory substances in the serum which they called antihormones. Since then investigators have asked whether antihormones are antibodies in an immunological sense or whether they are antagonistic hormones. Evidence has been presented (9 investigations cited) to support each view but the stronger evidence is in favor of the conclusion that antihormones are true antibodies. The controversy will not be settled until there is a visible in vitro reaction of the antihormone with the hormone (antigen) which has stimulated its formation.—*J. B. Paton (courtesy Biol. Abstracts).*

BACHMAN, C.

The normal excretion of estrogen and pregnanediol preceding normal parturition. *Am. J. Obst. & Gynec.* 42: 599, 1941.

Urinary estrogen and pregnanediol excretion was studied frequently during latter part of pregnancies of 6 women. These data did not permit a prediction of the date of labor.—*E.C.H.*

CORNBLEET, T., AND B. BARNES.

Androgen and the xanthomatoses. *Arch. Dermat. & Syph.* 44: 248. 1941.

Seven subjects with a variety of lipoidoses excreted normal quantities of urinary 17-keto-steroids as measured by a modification of the method of Dingemanse.—*I. C. Winter (courtesy Biol. Abstracts).*

FLUHMANN, C. F., AND K. M. MURPHY.

Endocrine factors in secondary amenorrhea. *Am. J. Obst. & Gynec.* 42: 565. 1941.

Clinical correlational studies of 73 women, aged 15 to 38 years, with secondary amenorrhea are reported. Forty-four per cent of 66 patients had B.M.R.'s ranging from −10% to −27%. Blood estrogens were studied in 52 patients: negative results were obtained in only 2 patients; cyclic increases were encountered in 46 patients. Excessive blood gonadotropins were found in 20% of 34 women.—*E.C.H.*

GRAY, L. A.

Clinical evaluation of equine gonadotropin. *Am. J. Obst. & Gynec.* 43: 387. 1942.

Results of equine gonadotropin therapy of 83 patients are reported: of 16 patients with amenorrhea or infrequent bleeding treated, 12 experienced episodes of bleeding during therapy, which, in 6 patients, were associated with varying secretory responses of the endometriums; of 27 patients with prolonged and/or excessive bleeding from estrogenic endometriums treated, 5 patients experienced varying degrees of secretory alteration in their endometriums and 11 patients noted some improvement in bleeding; of 30 patients with dysmenorrhea treated, 21 were judged to have been improved; of 10 men with decreased seminal values treated, 5 were judged improved.—*E.C.H.*

GREENE, R. R.

Reactions to estrogens. *Am. J. Obst. & Gynec.* 42: 858. 1941.

Thirty-nine menopausal patients, 37 of whom had been treated previously with diethylstilbestrol propionate, were treated with estradiol carbethoxylate. The incidence of undesired and untoward responses was essentially the same from each medication.—*E.C.H.*

HOLLENBECK, Z. J. R., AND P. J. REEL.

The use of stilbestrol in the management of the menopause. *Am. J. Obst. & Gynec.* 43: 331. 1942.

119 patients were treated. Dosages ranged from 0.05 mg. to 2 mg. daily for oral use and from 0.1 mg. to 15 mg. per week for parenteral use. Postmenopausal bleeding occurred in 2 instances and nausea in 23 patients.—*E.C.H.*

IVY, A. C.

Internal secretions of the gastrointestinal tract. *J. Am. Med. Assoc.* 117: 1013. 1941.

The endocrine secretions discussed are gastrin, secretin, cholecystokinin, enterogastrone, enterocrinin, villinkinin, and duodenin. The evidence for these possible secretions is reviewed.—*C.P.*

KUNSTADTER, R. H.

Adiposogenital dystrophy. *J. Am. Med. Assoc.* 117: 1947. 1941.

The author emphasizes that not all obese children outgrow their fatness, and not all children with hypogenitalism improve spontaneously. The history, physical examination, and laboratory tests must be evaluated properly

before instituting endocrine therapy. The objective therapeutic response to thyroid may be necessary to establish a diagnosis, although congenital absence or disease of certain elements of the anterior pituitary may nullify the effect of thyroid even in a hypothyroid child. Treatment of all forms of childhood hypothyroidism should be early, adequate, and persistent.—*C.P.*

Lass, P. M.

The inhibition of lactation during the puerperium by methyl testosterone. *Am. J. Obst. & Gynec.* 43: 86. 1942.

Twenty-five patients were treated. The usual regime of therapy embraced the oral administration of 30 mg. of methyl testosterone every 3 hours for 5 doses, treatment beginning 36 hours after delivery; subsequently 20 mg. were given every 3 hours for an additional 5 doses. It is reported that this treatment was effective in 'drying-up' breasts.—*E.C.H.*

Novak, E.

Gynecologic problems of adolescence. *J. Am. Med. Assoc.* 117: 1950. 1941.

The problems discussed are abnormal height, dysmenorrhea, amenorrhea, functional bleeding, obesity, hirsutism, and breast abnormalities.—*C.P.*

Paine, A. K.

Pathology of the embryo and abortion. *Am. J. Obst. & Gynec.* 43: 245, 1942.

This deals in general with the causes and treatment of abortion.—*E.C.H.*

Ripley H. S., and G. N. Papanicolaou.

The menstrual cycle with vaginal smear studies in schizophrenia, depression and elation. *Am. J. Psychiat.* 98: 567. 1942.

Observations were made on 817 menstrual bleedings of 221 patients suffering from schizophrenic and affective disorders. A more detailed study has been made in 31 cases by an analysis of the vaginal smears. A greater irregularity in menstrual interval than in a comparable normal group was found. A tendency to a delay, a weakened expression, or a temporary suppression of the follicular reaction was noted. Prolongation of the menstrual interval or amenorrhea was frequent. Short cycles also were observed. All these abnormalities are interpreted as the result of an adverse effect upon the growth of the ovarian follicles. A correlation between the severity of the illness and the degree of abnormality of the menstrual cycle was found. An improvement in the mental condition was usually accompanied by a change to a more normal menstrual function. The existence of an etiological relationship could not be ascertained.—*Author's abstract.*

Ross, R. A., E. C. Hamblen, W. K. Cuyler and M. Baptist.

Evaluation of colorimetric quantitation of 17-ketosteroids. Application to gynecology. *Am. J. Obst. & Gynec.* 42: 607. 1941.

A summary of the data secured from the quantitation of 5,700 24-hour specimens of urine of 216 women for 17-ketosteroids is reported. Theories in regard to adrenal hyperactivity sequential to intercurrent estrogenic failure and to climacteric ovarian failure are advanced. Practical diagnostic and prognostic data may be secured by these quantitations in some virilizing syndromes and in severe intercurrent estrogenic failure.—*E.C.H.*

Rudolph, G. de M.

The experimental effect of sex-hormone therapy upon anxiety in homosexual types. *Brit. J. M. Psychol.* 18: 317. 1941.

Chorionic gonadotropin (antuitrin S) was administered to 4 homosexual patients, 2 men and 2 women, suffering from anxiety. One was given testosterone propionate (testoviron) later. All the patients had had varying periods of psycho-therapy, with small success. Marked improvement of the anxiety occurred during the administration of 6 to 13 injections of chorionic gonadotropin over varying lengths of time. A similar result occurred in 1 man who was given two courses of testosterone propionate, of 7 doses each. There was some change in those secondary sex characteristics which had shown some abnormality. The anxiety returned at periods of from a few days to four months after the cessation of treatment. The author concludes on the basis of this experience that anxiety in predominantly homosexual patients may be directly dependent on deficiency of "sex hormone."—*Abst., Arch. Neurol. & Psychiat.* 46: 1090. 1941.

Salmon, U. J., R. I. Walter and S. H. Geist.

The use of estrogens in the treatment of dysuria and incontinence in postmenopausal women. *Am. J. Obst. & Gynec.* 42: 845. 1941.

Sixteen postmenopausal women with frequency, urgency and incontinence were treated intramuscularly with estrogens. All but 3 were relieved of symptoms. It is suggested that estrogenic therapy be tried in postmenopausal women prior to vaginoplasty or urethroplasty for urinary symptoms.—*E.C.H.*

Schoeneck, F. J.

Gonadotropic hormone concentration in emesis gravidarum. *Am. J. Obst. & Gynec.* 43: 308. 1942.

Studies, based upon the use of a quantitative Friedman test, are reported upon 173 patients distributed as follows: 72 patients without nausea and vomiting; 62 patients with 'physiologic' vomiting; 24 patients with 'excessive nausea and vomiting'; and 15 patients with 'pernicious' vomiting. The data obtained indicate that increased urinary gonadotropin values are associated with nausea and vomiting of pregnancy.—*E.C.H.*

Soule, S. D.

Anhydro-hydroxy-progesterone in threatened interruptions of pregnancy. *Am. J. Obst. & Gynec.* 42: 1009. 1941.

Twenty patients were treated with anhydro-hydroxy-progesterone and progesterone; only 4 miscarried. It is concluded that anhydro-hydroxy-progesterone is a valuable medication under these circumstances.—*E.C.H.*

STILES, M. H.

Basal metabolic rate in low grade chronic illness. A statistical analysis of 166 cases. *Am. J. Clin. Path.* 11: 871. 1941.

One hundred sixty-six individuals with low grade chronic illness had a mean B.M.R. of −8. The mean B.M.R. was lower in males than in females, although the difference was insignificant. Individuals below the age of 20 showed a more marked decrease of B.M.R. Patients with moderately severe or severe symptoms showed significantly lower rates than those with mild symptoms.—*E.v.H.*

WEISMAN, A. I., A. F. SYNDER AND C. W. COATES.

The 'Frog' test (Xenopus laevis) as a rapid diagnostic test for pregnancy. *Am. J. Obst. & Gynec.* 43: 135. 1942.

Diagnoses in 53 tests using the South African clawed frog were 100% correct. Technic for the test is described. —*E.C.H.*

ADRENALS

HARTMAN, F. A.

The adrenal hormones in medical practice. *J. Am. Med. Assoc.* 117: 1405. 1941.

The adrenal cortical hormone is discussed under the following headings: electrolyte metabolism, general metabolism, carbohydrate metabolism, and the relationship to vitamins, pigmentation, lactation, and the central nervous system. The treatment of Addison's disease is outlined in detail.—*C.P.*

PATTERSON, J., I. M. MCPHEE AND A. W. GREENWOOD.

17-Ketosteroid excretion in adrenal virilism. *Brit. M. J.* 1: 35. 1942.

By the modification employed, the 17-ketosteroid excretion expressed as milligrams of androsterone per 24 hours were found to be as follows: 12 normal women 3.5 to 14.6, average 7.4; 9 normal men 9.4 to 20.9, average 13.3. There was a positive correlation with body weight in both men and women, but no change was observed with the menstrual cycle in 15 determinations on one individual. The values were distinctly elevated in 4 cases of adrenal cortical tumors (27–270), and in 7 cases of adrenal hyperplasia (primary or prepubertal virilism) (34–64), but not in 21 cases of secondary or post-pubertal virilism (9.0–33.4). No distinct changes in 17-ketosteroid excretion were noted in 3 feminized males, nor in hypogonadism, homosexuality, and hypopituitarism. The cases classified by the authors as secondary virilism exhibited hirsutism with or without menstrual disturbances but no mention is made of other signs of masculinization, e.g., enlargement of the clitoris. Consequently these cases are probably ones which are usually classified under the heading 'hirsutism without true masculinization' and thus the low values found in this group assume diagnostic importance.—*E.B.A.*

WILSON, D. M., F. J. ROBINSON, M. H. POWER, AND R. M. WILDER.

Diagnosis of Addison's disease. Further experience with the Cutler-Power-Wilder sodium chloride restriction test. *Arch. Int. Med.* 69: 460, 1942.

The results of examination of 63 patients by means of a 52 hour salt restriction procedure are reported. Of 16 patients with Addison's disease, symptoms of crisis which necessitated discontinuance of the test developed in 10; 5 patients responded with the typically high concentrations of chloride and sodium in the final 4 hour specimen of urine, while 1 patient who responded atypically had concentrations of sodium and chloride in the plasma sufficiently low to be diagnostically significant. With 1 exception 44 patients not having Addison's disease responded with typically low concentrations of sodium and chloride in the final 4 hour specimen of urine. In the exception noted normal concentrations of sodium and chloride in the plasma and the failure of the patient to react unfavorably to a prolongation of salt restriction aided in the exclusion of the diagnosis of Addison's disease. Three patients who had Addison's disease treated with desoxycorticosterone acetate through the test procedure responded similarly to that of subjects who did not have Addison's disease. The test subjects the patient who has Addison's disease to some danger. Its chief value lies in the diagnosis of or exclusion of adrenocortical insufficiency when uncertainty exists. The clinician who subjects a patient to this test should be prepared to recognize and treat acute adrenal cortical insufficiency should it occur. —*I.B.*

GONADS

BICKERS, W.

Uterine contractions in dysmenorrhea. *Am. J. Obst. & Gynec.* 42: 1023. 1941.

Uterine contractions in 15 women, aged 16 to 26 years, with severe dysmenorrhea were studied by the intrauterine balloon method and recorded kymographically. High amplitude contractions characterized dysmenorrhea. Progesterone and testosterone did not alter these contractions; the administration of estrogens during the early part of the cycle reduced contractions and pain.—*E.C.H.*

EDITORIAL.

Climacteric in aging men. *J. Am. Med. Assoc.* 118: 456. 1942.

This editorial reviews the evidence for a climacteric in the male. Arguing by analogy with the female sex cycle and with the knowledge of the effects of castration in the male, no definite data for such a climacteric are available.—*C.P.*

FARROW, J. H., AND HELEN Q. WOODARD.

The influence of androgenic and estrogenic substances on the serum calcium. *J. Am. Med. Assoc.* 118: 339. 1942.

Testosterone propionate therapy was given to 33 female patients with breast cancer metastases to bone. Unlike castration of these patients, the testosterone accelerated the growth of the metastases. The serum Ca was elevated (perhaps indirectly) by the therapy.—*C.P.*

GEIST, S. H., J. A. GAINES AND U. J. SALMON.

The effect of gonadotropins upon the human ovary *Am. J. Obst. & Gynec.* 42: 619. 1941.

The ovaries of 91 women, aged 25 to 50 years (52 of whom were past 40 years of age), were studied at operations following varying dosage schedules of the following gonadotropins or combinations of them: pituitary; chorionic; equine; chorionic and pituitary; chorionic and equine; and chorionic and diethylstilbestrol. In no instance could the occurrence of ovulation be related to the therapy.—*E.C.H.*

GEIST, S. H., AND U. J. SALMON.

Androgen therapy in gynecology. *J. Am. Med. Assoc.* 117: 2207. 1941.

Therapeutic effectiveness of androgens in the female stems from their ability *a*), to nullify or modify the action of estrogens, *b*), to suppress or decrease the production of estrogens by the ovary, *c*), to inhibit the proliferative processes in the endometrium, *d*), to inhibit the reactivity of the uterine musculature, and *e*), to inhibit the gonadotropic activity of the hypophysis.—*C.P.*

GREENBLATT, R. B.

Histologic changes in the ovary following gonadotropin administration. *Am. J. Obst. & Gynec.* 42: 983. 1941.

Thirty-six women, aged 15 to 49 years, were treated preoperatively with diverse gonadotropins and their ovaries subsequently were studied at operation. The production of corpora lutea was more common following the use of a mixture of pituitary 'synergist' and chorionic gonadotropin. Regardless of what gonadotropin was used follicular atresia was the most commonly encountered finding.—*E.C.H.*

HAMBLEN, E. C.

Uses and limitations of estrogens in gynecic practice *J. Am. Med. Assoc.* 117: 2205. 1941.

Practical estrogen therapy is discussed under the following headings: therapy of ovarian failure, therapy of local hypoplasias, estrogenic therapy to depress other glands, local vaginal effects, and empiric uses.—*C.P.*

HENDERSON, D. N.

Granulosa and theca cell tumors of the ovary. *Am. J. Obst. & Gynec.* 43: 194. 1942.

The clinical records and pathologic findings of 30 patients with ovarian tumors of granulosa or theca cell type are reported.—*E.C.H.*

JOHNSTON, J. A.

Factors influencing retention of nitrogen and calcium in period of growth. IV. Effect of estrogen. *Am. J. Dis. Child.* 62: 708. 1941.

The report deals with continuous balance studies on N and Ca and determination of the B.M.R. on 6 girls at puberty. Estrone was administered to 5 in doses varying from 12,000 to 36,000 U and diethylstilbestrol to one. A depression of the Ca balance in both the urinary and fecal fractions was obtained in 5 and an additional N depression in 3 with the estrone. Diethylstilbestrol likewise resulted in a diminution of both Ca and N.—*M.B.G.*

KENNY, M., AND D. DALEY.

Experience with the intravenous use of the follicle-stimulating hormone of the anterior pituitary in menstrual disorders. *Proc. Roy. Soc. Med.* 34: 804. 1941.

The authors used a preparation of pregnant mare's serum intravenously in 3 types of menstrual disorders: (1) Metropathia hemorrhagica. In 3 of 4 cases regular menstruation was induced. Doses of 500 units were given intravenously on 3 successive days. In 2 of these cases ovulation was produced as judged by the finding of secretory endometrium at the succeeding menstrual period. (2) Menorrhagia with ovulation. Very doubtful results were obtained in 2 cases of this type tried. (3) Secondary amenorrhea. One of 3 cases seemed to respond but biopsy confirmation of ovulation was not possible.—*J.E.H.*

MARWIL, T. B., AND D. C. BEAVER.

Brenner tumor of the ovary associated with uterine bleeding. *Am. J. Obst. & Gynec.* 43: 99. 1942.

A Brenner ovarian tumor in a woman 77 years of age was associated with vaginal bleeding and a slightly hyperplastic estrogenic endometrium.—*E.C.H.*

NOVAK, E., AND E. H. RICHARDSON, JR.

Proliferative changes in the senile endometrium. *Am. J. Obst. & Gynec.* 42: 564. 1941.

One hundred and thirty-seven endometriums from women 2 to 40 years past menopause were studied. Less than one-half of these was atrophic. Forty-two showed proliferative activity: moderate in 14, marked in 28. It is suggested that the adrenals are the source of the postmenopausal estrogen operative in these cases.—*E.C.H.*

SALMON, U. J., S. H. GEIST AND R. I. WALTER.

Treatment of the menopause. *J. Am. Med. Assoc.* 117: 1843. 1941.

Implantation with loose crystals and compressed pellets of α-estradiol, α-estradiol benzoate, and α-estradiol dipropionate was carried out on a series of 180 patients. A control series of 18 menopausal patients was given a single injection of comparable amounts of estrogen in solution in oil. The implantation of estrogens in the form of loose crystals or compressed pellets was more efficient than the injection of comparable amounts of hormone in oil. Loose crystals of α-estradiol and α-estradiol benzoate were more effective than the compressed pellets of the same chemical constitution. The longest period of symptomatic relief was obtained by the implantation of α-estradiol crystals—*C.P.*

SCHAUFFLER, G. C.

Double uterus with pregnancy. *J. Am. Med. Assoc.* 117: 1516. 1941.

The author's experience with 11 cases of double uterus is reviewed through 32 pregnancies. Symptoms may be irregular menstruation, dyspareunia, repeated abortion, or malposition of the fetus.—*C.P.*

VEST, S. A., AND B. BARELARE, JR.

Peroral use of methyl testosterone. *J. Am. Med. Assoc.* 117: 1421. 1941.

Methyl testosterone per os was effective in 2 patients